

SOME SYNTHETIC AND COMPARATIVE ASPECTS
OF YLIDE INTERMEDIATES : CYCLOIMMONIUM,
PHOSPHORUS YLIDES AND π -SULFURANES

A Thesis

Submitted for the degree of
Doctor of Philosophy

IN
CHEMISTRY

OF
Bundelkhand University
JHANSI

Under The Supervision Of
Dr. K. C. GUPTA

Ph. D.

BY

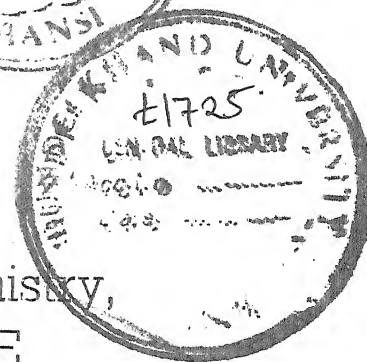
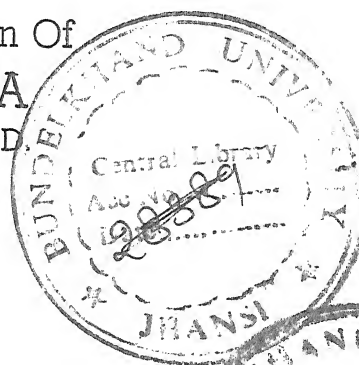
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HUMBLY AND RESPECTFULLY

DEDICATED TO

THE SACRED MEMORY

OF

MY BELOVED PARENTS

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DATED : 21-12-1990



(SURESH CHANDER KHURANA)

C E R T I F I C A T E

Certified that the thesis entitled,
"SOME SYNTHETIC AND COMPARATIVE ASPECTS OF YLIDE
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AND Λ -SULFURANES" by Mr. Suresh Chander Khurana
embodies the work carried out by him under my
supervision and that this work has not been
submitted elsewhere for a degree. Mr. Khurana has
put in more than 200 days attendance in the
laboratory during this work.

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CHAPTER - I

SOME SYNTHETIC AND COMPARATIVE ASPECTS OF YLIDE INTERMEDIATES: CYCLOIMMONIUM, PHOSPHORUS YLIDES AND π -SULFURANES

GENERAL SURVEY

* * *

SOME SYNTHETIC AND COMPARATIVE ASPECTS OF YLIDE INTERMEDIATES:
CYCLOIMMONIUM, PHOSPHORUS YLIDES AND π -SULFURANES

1.1 GENERAL SURVEY :

The term 'ylide' is used in synthetic Organic Chemistry for a new and unique class of 'Zwitterionic' compounds which have an anion covalently bonded to a positively charged heteroatom. In order to explain their behaviour, the ylides may be considered to be the resonance hybrids of two limiting structures Ia which represents the 'ylide' form and Ib which represents the 'ylene' form. In the ylide form, the dipolar zwitterionic structure involving an onium centre at elements like N, P, As, S, Sb, Bi, Se, Ni etc. is the predominant feature. In this structure, the onium centre is situated next to a carbanionic function which is, at least partially, delocalized into suitable substituents. The ylene form, on the other hand, has a true double bond between the onium centre and the ylidic carbon. It is this form which, in effect, reduces or may even totally eliminate the formal charge associated with these atoms.¹⁻²

Of the two forms discussed above, it is the ylide form which is predominant in the ground state. This has been made increasingly clear by the application of a number of modern analytical techniques and theoretical computations.³⁻⁵

Indeed, most of the early investigators used this form i.e. the ylide description to successfully explain structures, reactivity and reaction mechanisms.^{2,6} Therefore, the present day description of the species as ylides is fully justified and is extensively used in chemical literature.

The properties of the carbanion and the possible involvement of the heteroatom determine the reactivity of the molecule and the extent of $d\pi-p\pi$ bonding largely determine the stability of this class of compounds. Using the rates of alkali catalysed exchange of the α -hydrogen atom, it has been possible to make a comparison⁷ of the stability of ylides formed by different elements. It is beyond doubt that the change in structure greatly affects the acidic nature of the salt.

An established classification of ylides is based on the following two factors:-

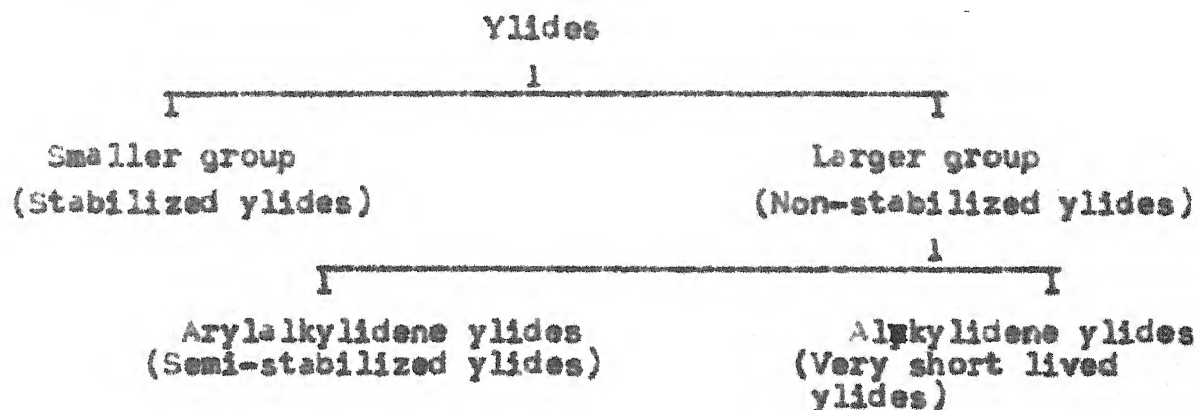
- (i) stability
- (ii) the ease with which they react with electrophilic substrates.

On the basis of the above classification, a group of ylides called the 'non-stabilized ylides' comprises a very large number of such species. These ylides are generated in solution from their salts and are not isolable due the

absence of stabilising factors. Thus, they undergo reaction 'in situ'. These ylides are sub-divided into two categories depending upon whether alkyl or arylalkyl groups are bonded to the heteroatom. Of these, arylalkylidene ylides, referred to as semistabilized ylides, can not be isolated but persist in solution for a considerable time. The alkylidene ylides are, however, very short lived.

The second but a much smaller group of ylides comprises the 'stabilized ylides'. This group of ylides, as their name implies, are comparatively more stable. These ylides can be isolated, purified and stored for a considerable period. The attachment of the electron withdrawing groups with ylidic carbanion is responsible for the stability of this group of ylides.

Thus, the classification of ylides may be represented as follows:



In the recent years a large volume of research

on ylides has been devoted to explore their synthetic applications. It is now realised that this type of compounds has vast potential in the domain of synthetic Organic Chemistry. It is not without reason, therefore, that the studies on these reactive intermediates have expanded manifold to encompass the ylides of N, P, As, Sb, Bi, S, Se and Te by a large number of investigators producing monographs^{1-2,8-12} and review articles¹³⁻³⁷. These studies have resulted in the synthesis of a large variety of heterocyclic compounds, natural products, vitamins, hormones etc.

The involvement of a particular heteroatom markedly affects the behaviour of different types of ylides. The following sections are devoted to a brief review of these ylides.

1.2 CYCLOIMMONIUM YLIDES (PYRIDINIUM YLIDES) :

1.2.1 GENERAL REMARKS :

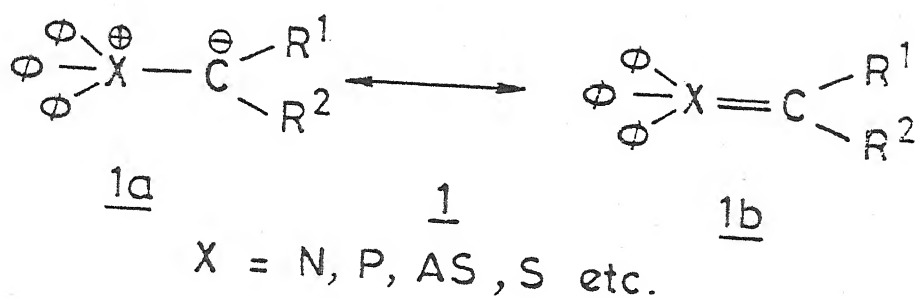
Among the nitrogen ylides, the most important type of cycloimmonium ylides- the subject of our present investigations - are the pyridinium ylides in which the cationic part is involved in the pyridinium ring.

Indeed, the pyridinium ylides and their salts form a special group of compounds having a normal covalent

bond between nitrogen and carbon atoms in which the free electron pair of the former can take part in N - C bond formation. Consequently, the nitrogen atom is forced to approach tetravalence (Scheme 1.1). In fact, Anderson's³⁸ pioneering researches in 1855 leading to the synthesis of ethylpyridinium iodide (2) by the interaction of pyridine with ethyl iodide initially paved the way for the synthesis of this class of compounds (Scheme 1.2).

The exploration of these salts and ylides has been and still is a challenge to modern Organic Chemist. A German Chemist F. Krohnke and his co-workers³⁹ must be given the credit due to them for initiating the investigations in this vital direction. They were able to isolate some pyridinium ylides while observed others in solution only. They laid greater emphasis on studying the reactivity of the pyridinium salts and their use to synthesise a large variety of compounds.

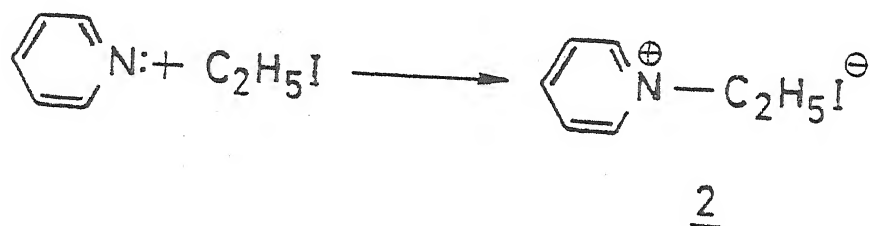
The reactivity of the pyridinium salts is attributed to the aromatic character of the pyridine heterocycle, its basicity and the electron withdrawing effect of the nitrogen atom in the pyridine ring. In addition, the electrophilic effect of nitrogen makes 2, 4 and 6 positions of the heterocycle relatively more electropositive. As a result, these positions are



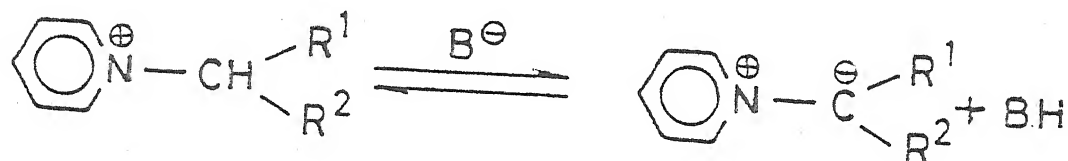
Scheme I-1



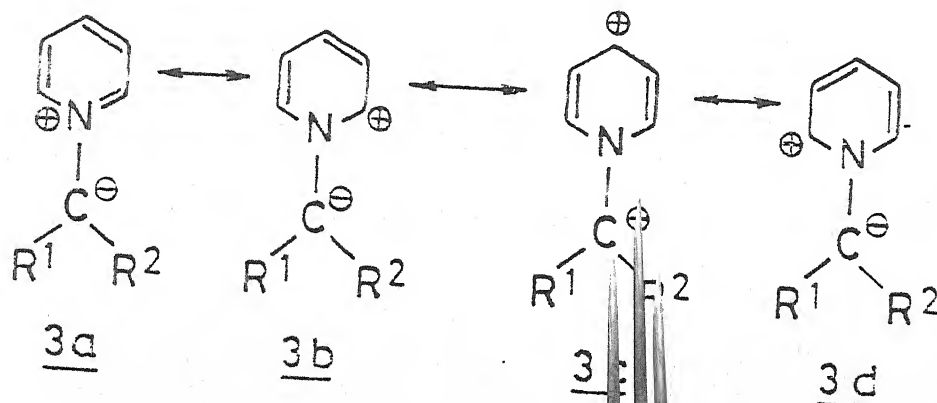
Scheme I-2

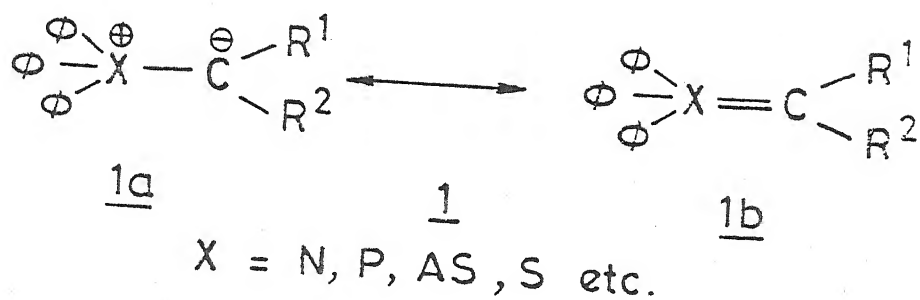


Scheme I-3



Scheme I-4

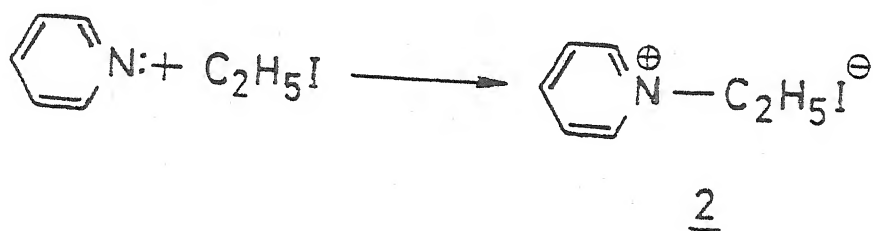




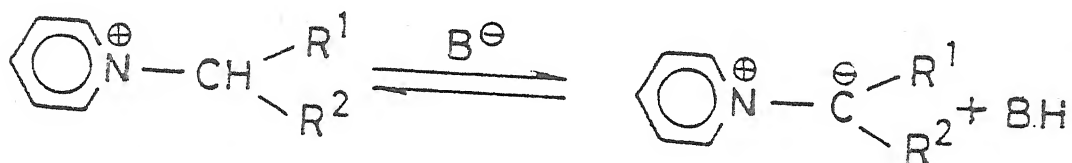
Scheme I-1



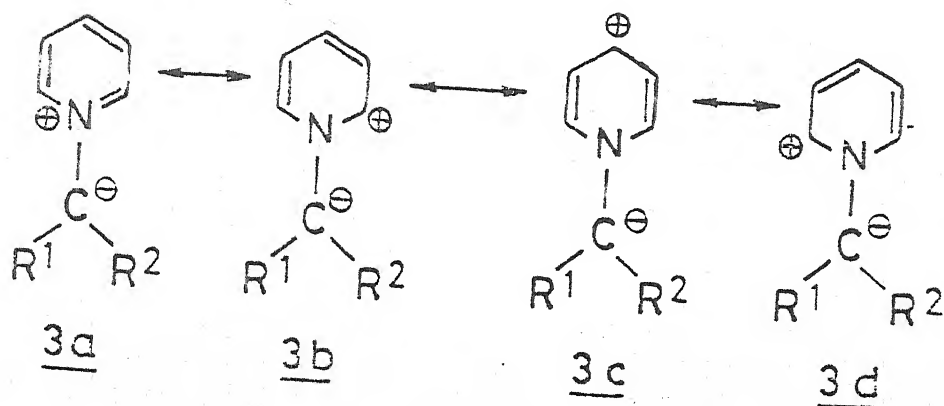
Scheme I-2



Scheme I-3



Scheme I-4



conveniently attacked by nucleophiles. The shortage of electron density at these positions further activates the hydrogen atoms of methyl, benzyl or other groups attached to the α -carbon. The consequent removal of the α -proton from the pyridinium salts results in the formation of highly reactive intermediates viz. pyridinium ylides (Scheme 1.3). On account of the inability of the nitrogen atom to expand its valence shell of electrons, the pyridinium ylides are comparatively more reactive than the phosphonium ylides. Obviously, therefore, the existence of the former in the ylene form is precluded.

The stability of the pyridinium ylides may be explained as follows:

There is extensive delocalization of the positive charge on the pyridine ring as represented by the various contributing structures (3a-d) (Scheme 1.4). There is also the carbanion participation in the resonance of the heteroatomic ring (4a-c). These two factors are mainly responsible for their stability. Of much less importance are Coulombic interactions for the stability of some ammonium ylides.

If it is assumed that there is only an electrostatic interaction between the carbanion and the onium group (4b), the electron pair of sp^3 hybridised ylidic

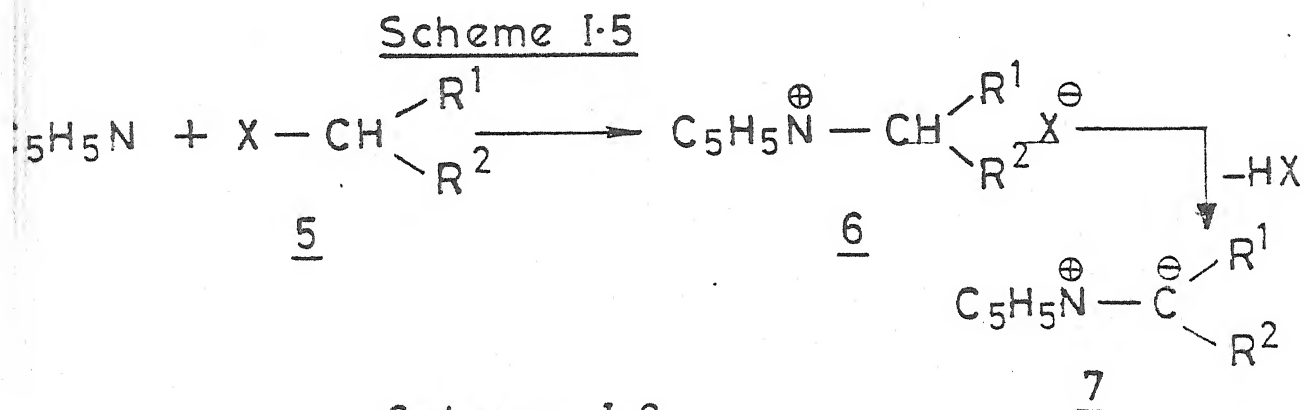
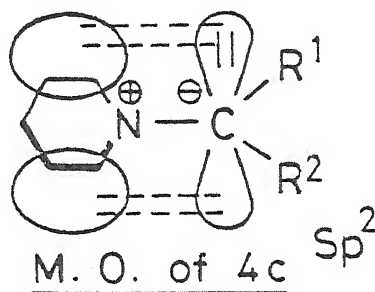
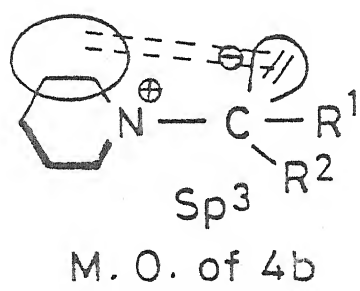
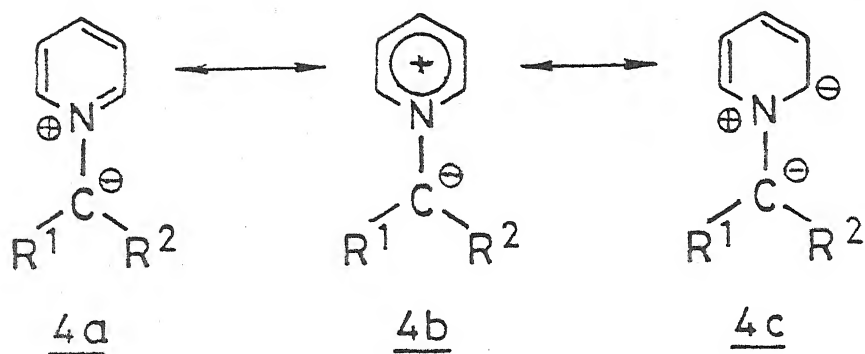
carbanion would be involved in a π D type of molecular orbital with sp^3 hybridised nitrogen atom of the pyridine ring. But overlapping is more effective if we consider the resonating form (4C) in which there is an interaction of the bielectronic p orbital with the π electrons of the pyridine ring. Consequently, the pyridinium ylides are stabilized. The nature of substituents, R^1 and R^2 attached to the ylide carbanion also influences the stability. In case these groups are electron withdrawing, additional resonance structures occur to reflect a marked sp^2 hybridisation of the ylide carbon through charge delocalisation.

The cycloimmonium ylides (which are pyridinium ylides), the main subject of our investigations, may be divided into five membered cyclo-immonium ylides and six membered cycloimmonium ylides which include azomethine and benzoazomethine as intermediates.

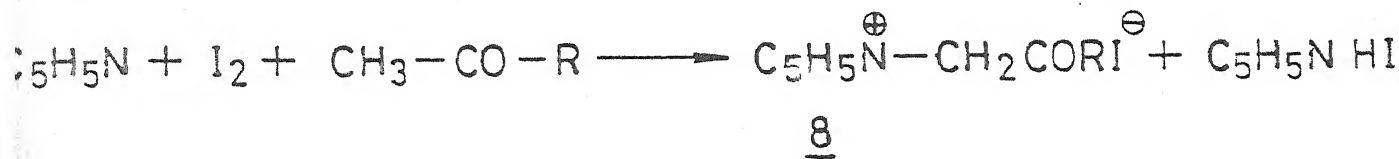
1.2.2 GENERATION OF PYRIDINIUM YLIDES:

(a) Ylides from pyridinium salts:

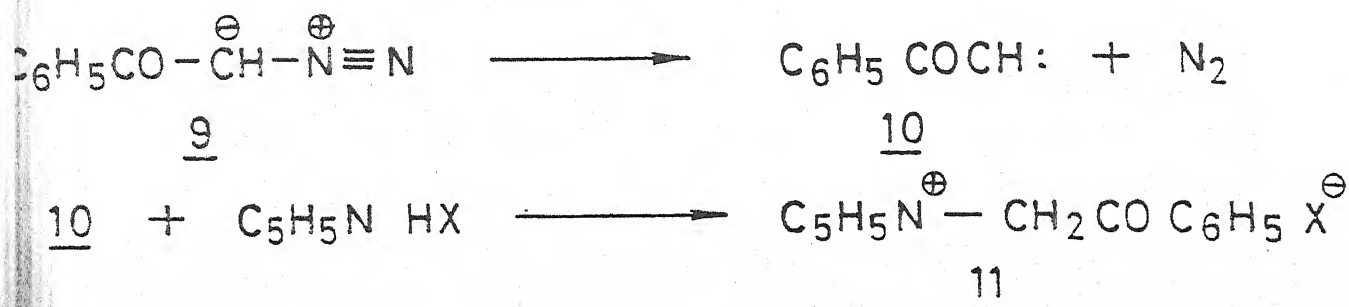
The pyridinium ylides are most commonly prepared by the quarternisation of pyridine with substituted alkyl halides (5) to give substituted alkylpyridinium halides (6) which on dehydrohalogenation with suitable bases yield pyridinium methylides⁴⁰ (Scheme I.5).



Scheme I.6



Scheme I.7



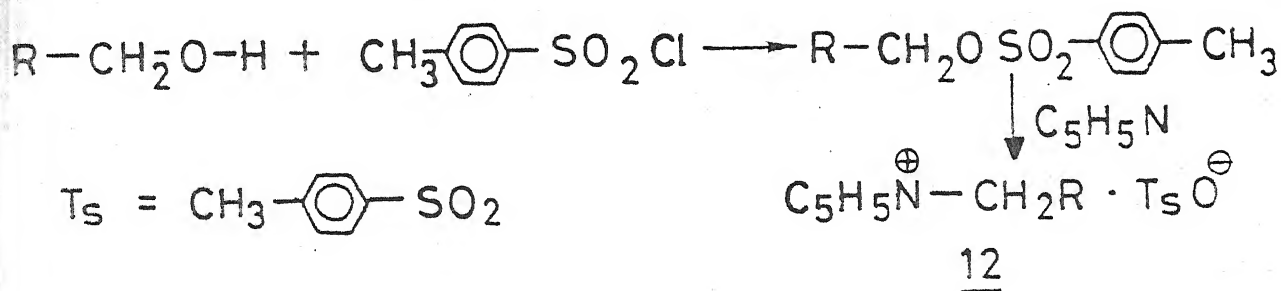
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Pyridinium salts can also be prepared by the quaternisation of pyridine with active methyl ketones and iodine⁴¹⁻⁴³ (Scheme 1.6). Other less important methods for the preparation of pyridinium salts involve the reaction of carbene intermediates (10) with pyridine hydrohalide (Scheme 1.7) and reaction of alcohol with tosyl chloride in presence of pyridine (Scheme 1.8).

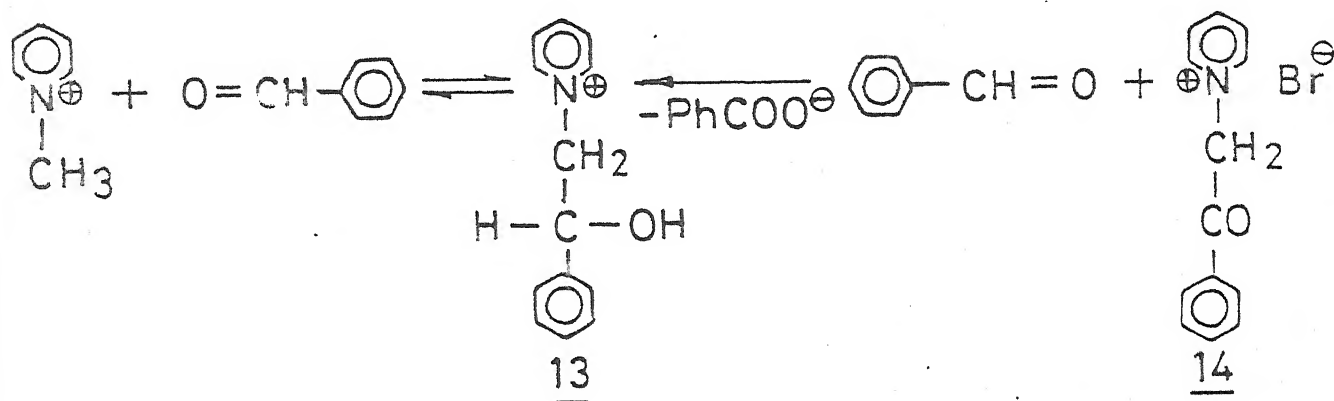
The reaction of 1-methyl - pyridinium salts with benzaldehyde in alcohol containing piperidine to form 1-(α -hydroxyphenylethyl) pyridinium salt (13) (Scheme 1.9) was studied by Krohnke et al.⁴³⁻⁴⁴ This salt (13) has also been synthesised by the reaction of phenacylpyridinium bromide (14) with benzaldehyde at 0°C in presence of piperidine or diethylamine (Scheme 1.9).

It is the usual practice to generate pyridinium ylides (15) by the action of suitable bases on the pyridinium salts (Scheme 1.10). The nature of substituents present on the α -carbon atom determines its acidity on which depends the strength of the base to be used for dehydrohalogenation of the corresponding pyridinium salt. In most cases the bases used are aqueous solutions of alkali carbonates or amines in anhydrous aprotic solvents.^{39,46-47} It is occasionally advantageous to use sodium hydride in dimethylformamide.⁴⁶⁻⁴⁷

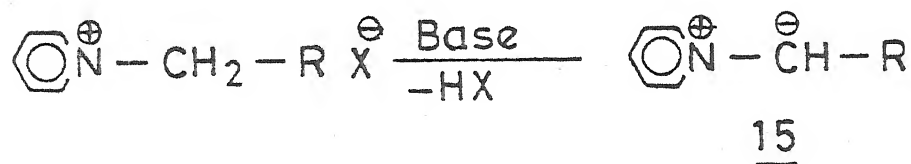
Scheme I-8



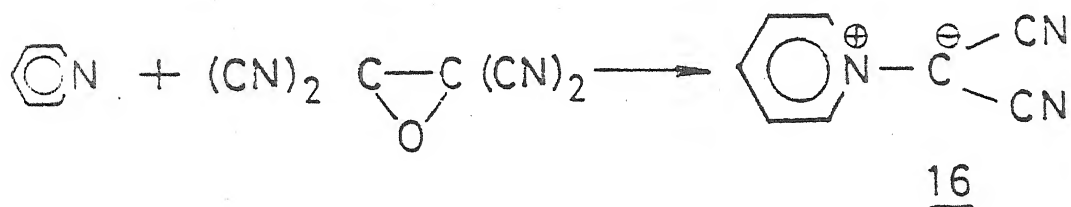
Scheme I-9



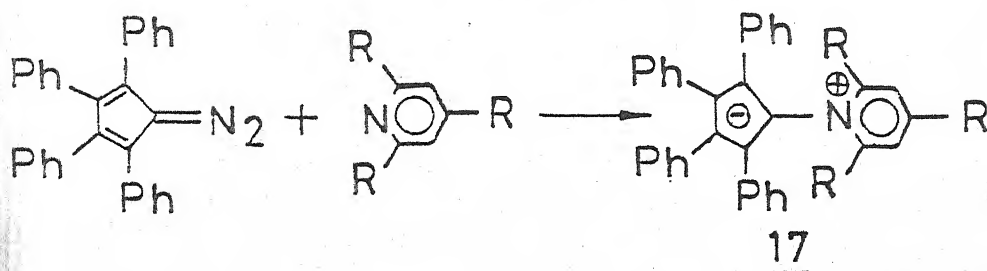
Scheme I-10



Scheme I-11



Scheme I-12



Most of the ylides so formed are not isolable and are extremely sensitive to environmental components. They are, therefore, generated in anhydrous medium under an inert atmosphere. It is the normal practice to carry out the reaction in non-polar solvents such as benzene. However, the use of polar solvents is not ruled out in some cases.⁴⁸⁻⁴⁹

(b) Ylides from pyridine and ethylene oxide :

Lin et al⁵⁰ and some other workers⁵¹ reacted tetracyanoethylene oxide with pyridine at Δ to afford a stable pyridinium dicyanomethylide (16) which had a high melting point (Scheme I.11).

(c) Ylides from diazo compounds and pyridine :

The irradiation of tetraphenyl or triphenyl-diazocyclopentadiene in pyridine under nitrogen atmosphere with a high pressure of mercury lamp through a pyrex filter yields pyridinium ylides⁵² (17) (Scheme I.12).

(d) Ylides from other pyridinium ylides :

Leonte and Zgravescu⁵³ have prepared dicyanopyridinium methylide (19) by heating cyanocarbonylpyridinium-methylide (18) with POCl_3 in presence of sodium pyrosulphite. On changing the dehydrating agent i.e. acetic anhydride

in place of POCl_3 , Cyanoacetylpyridiniummethyliide (20) was formed. The product (20) could also be prepared by the acetylation of (21). Alternately the ylide (19) could be produced by the reaction of bromocyanoacetic ester with carbalkoxypyridinium ylides (22) (Scheme I.13).

1.2.3 REACTIONS OF PYRIDINIUM YLIDES:

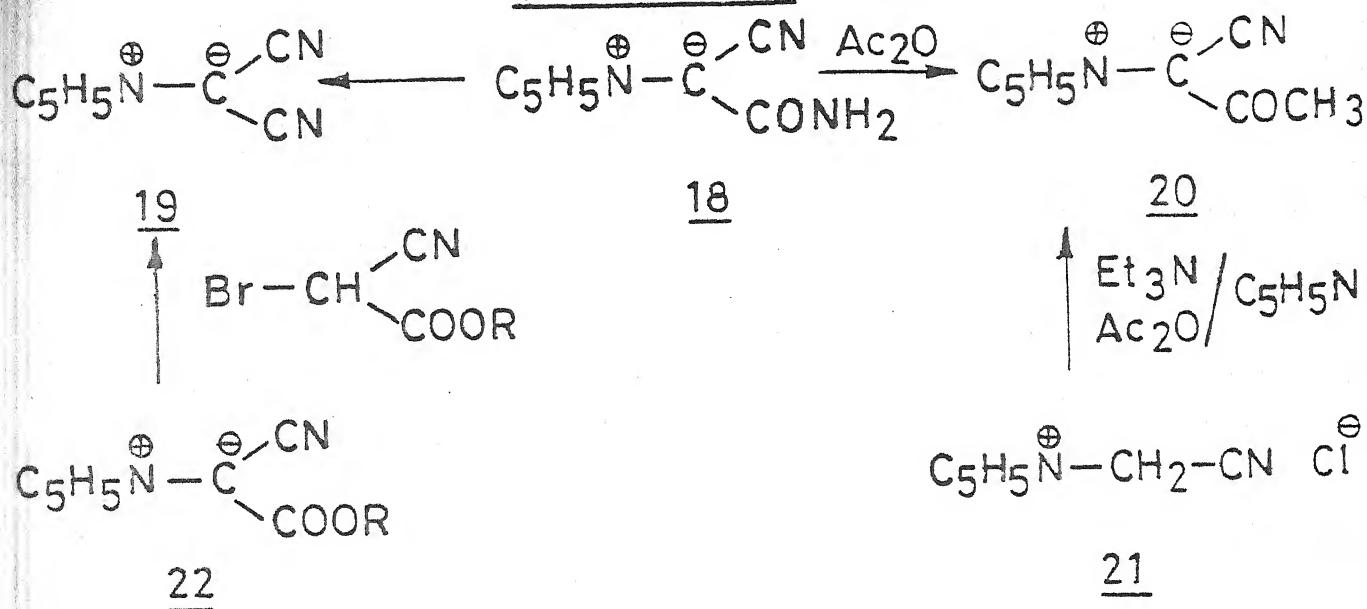
(a) Alkylation :

Pyridinium ylides, when subjected to alkylation, yield pyridinium salts. These salts, when treated with a base, give disubstituted pyridinium ylides⁵⁴ (23) (Scheme I.14). The alkylation of the ylide in the absence of a base leads to a complex overall reaction. Thus, the treatment of pyridiniumphenacylide (24) with phenacyl bromide yields several products⁵⁵ (26,27) (Scheme I.15) due to the possible interaction between the intermediates and the initial ylide and to the transylidation reactions and bond cleavage.

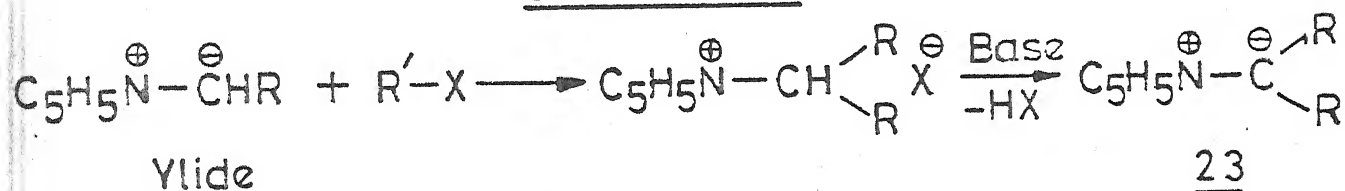
(b) Acylation :

Different acyl halides react with pyridinium ylides (28) to yield acylated pyridinium ylides (29) (Scheme I.16). The nature of the acylating agent used determines the course of reaction in each case. Thus, acylation of carbonyl stabilized pyridinium ylides (30 a-b) with benzoyl chloride yields O-acylated (31b) products⁶⁰

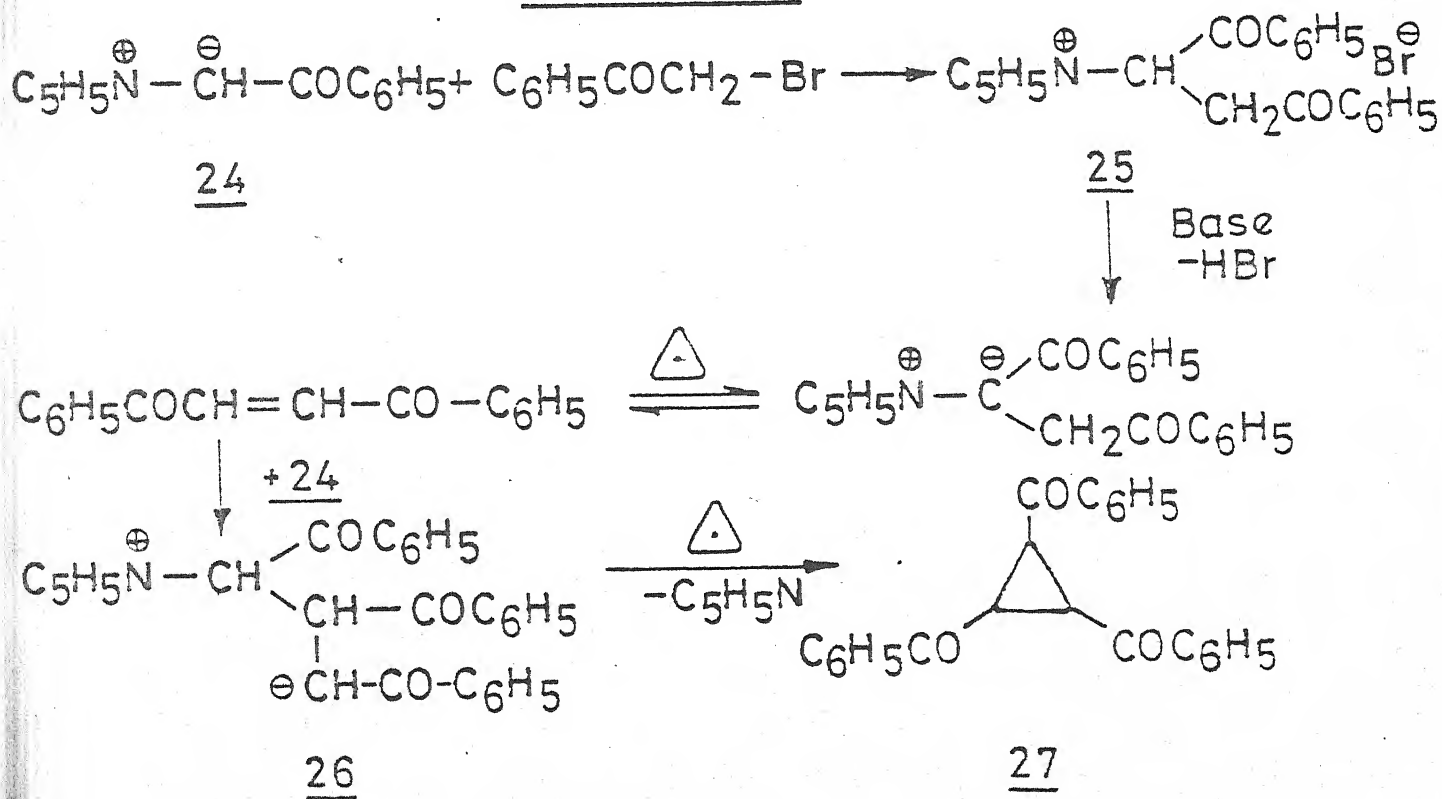
Scheme I-13



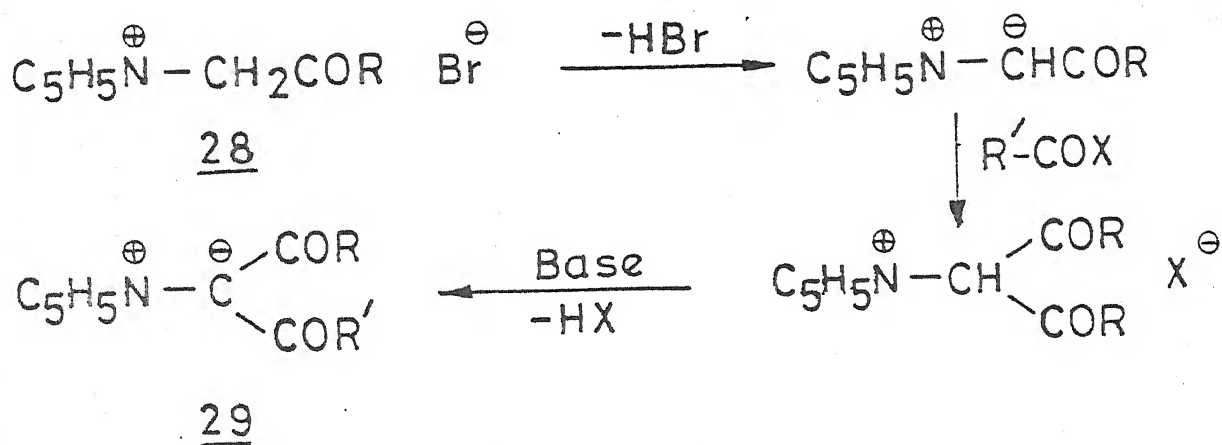
Scheme I-14



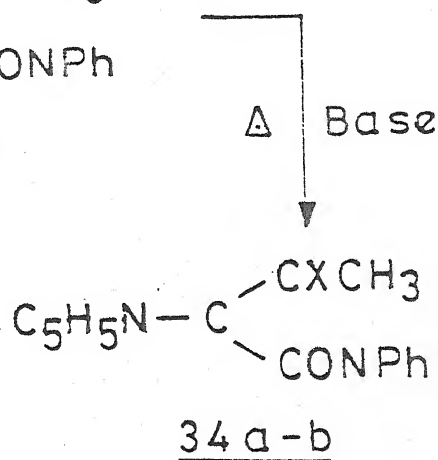
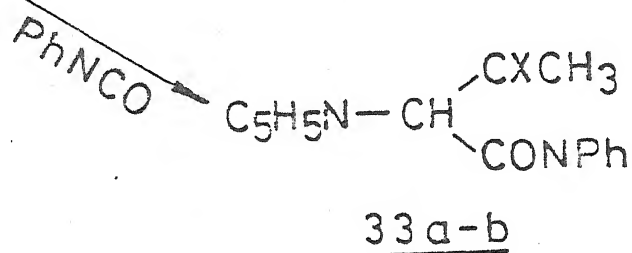
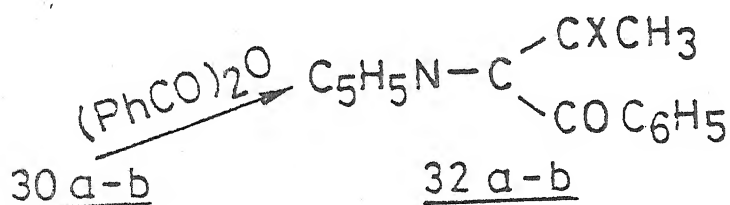
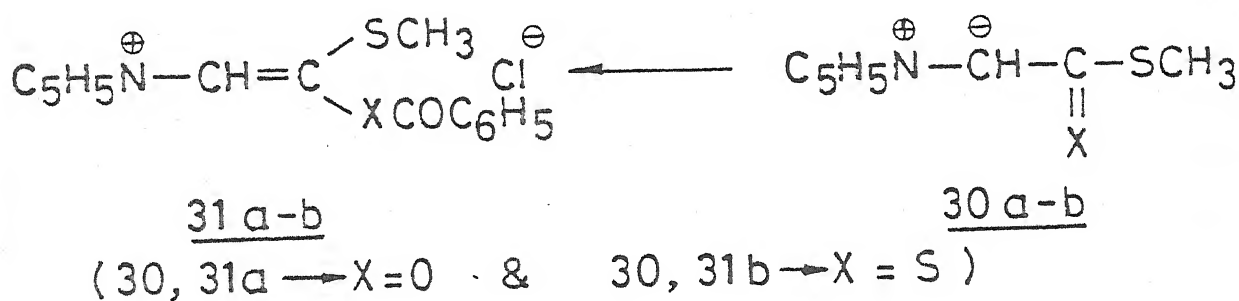
Scheme I-15



Scheme I-16



Scheme I-17



(Scheme I.17). However, acylation with benzoic anhydride leads to a different course to give C - acylated products (32 a-b) only^{46,47} (Scheme I.17). Similarly, phenylisocyanate followed C - acylation to yield a new ylide⁵⁶ (34 a-b) (Scheme I.17).

(c) Arylation :

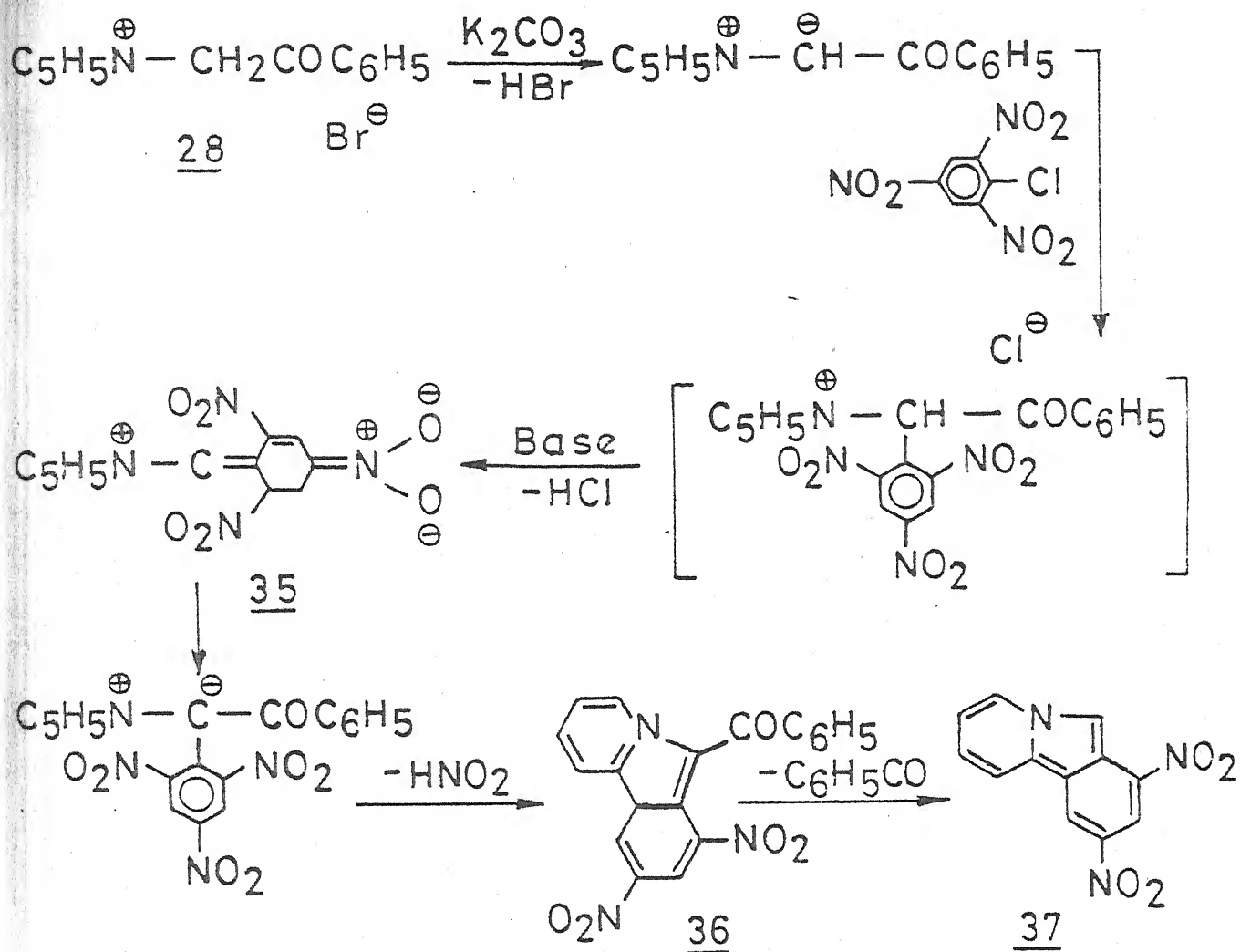
Arylation of pyridinium salts and ylides is a comparatively difficult process as aryl halides possess low reactivity. The reaction of picryl chloride with phenacylpyridinium bromide in basic medium forms (35) which, in strong alkaline medium, eliminates nitrous acid to yield a deep red indolizine compound (36) which itself eliminates a benzoyl group on heating in acidic medium to form a product (37)⁵⁷ (Scheme I.18).

N - phenacylpyridinium bromide may also similarly react with Chloranil to form a zwitter ion which undergoes cyclisation to yield the indolizines (38) and (39)⁵⁷ (Scheme I.19).

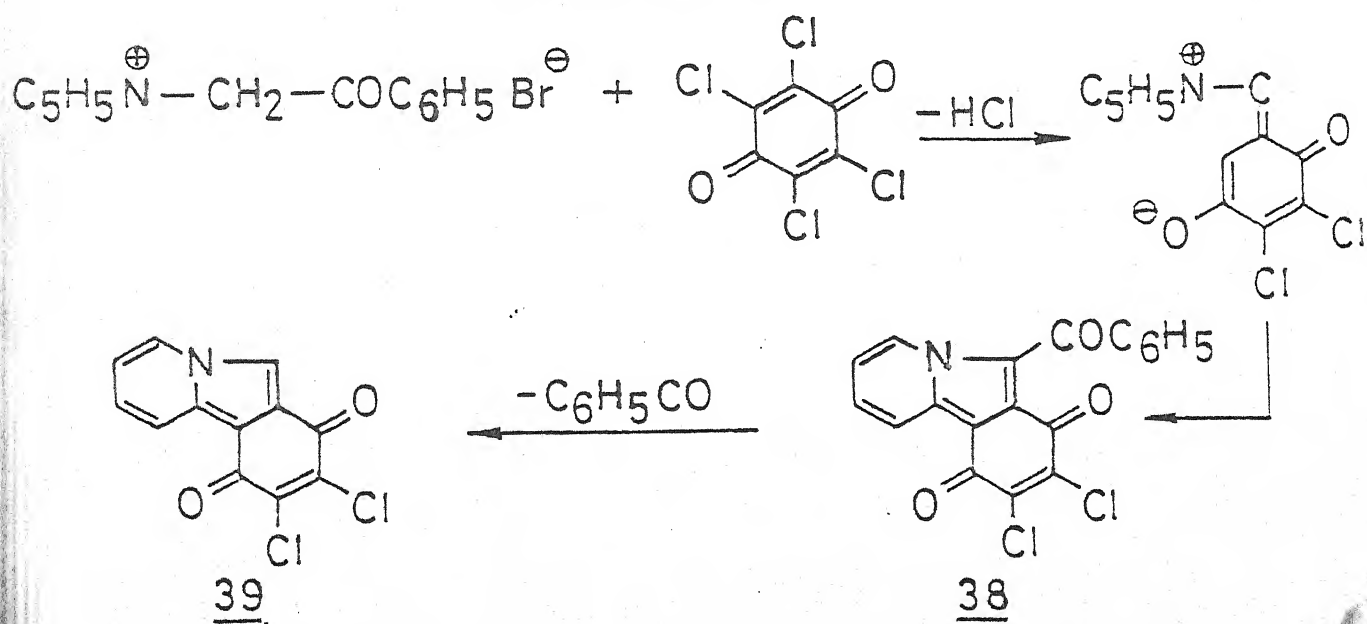
(d) Reactions with multiple bonds :

1. Reactions with aldehydes : Pyridinium ethanols⁵⁸ (41) are produced when pyridinium ylides (40) react with aldehydes (Scheme I.20). In case an acyl radical is attached to the ylide, it is cleaved during

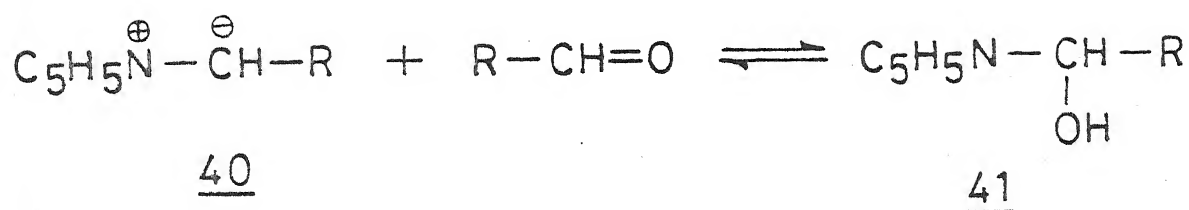
Scheme I-18



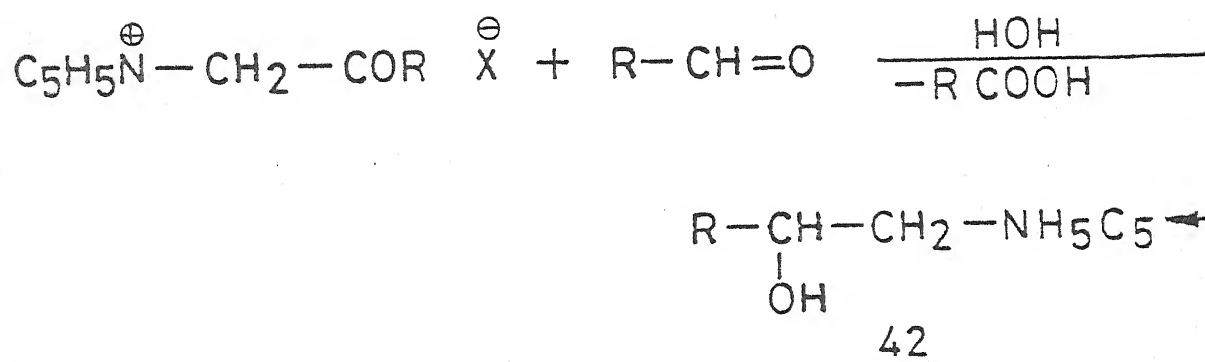
Scheme 1-19



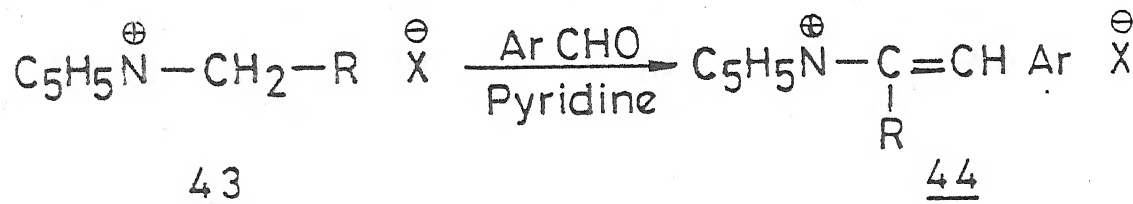
Scheme I-20



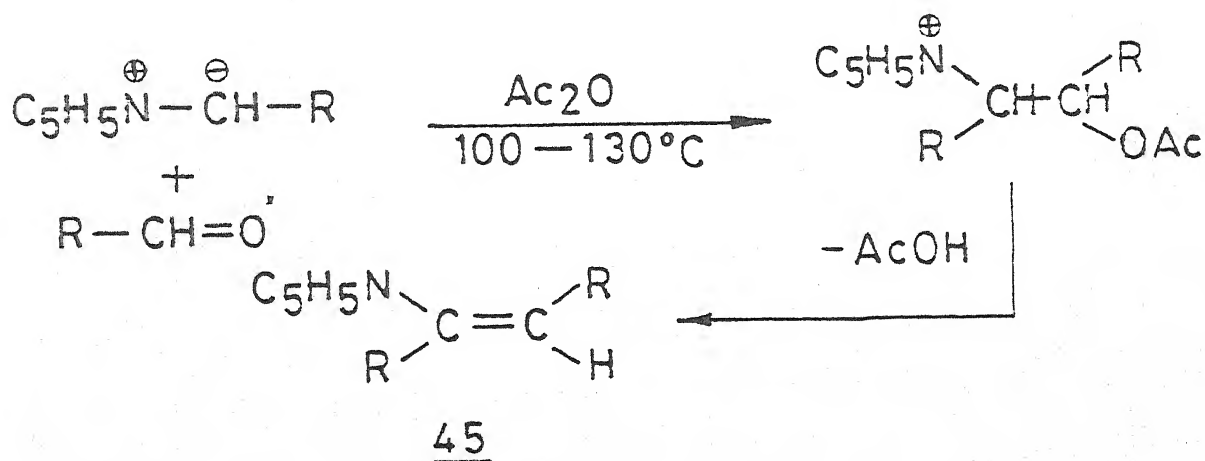
Scheme I-21



Scheme I-22



Scheme I-23



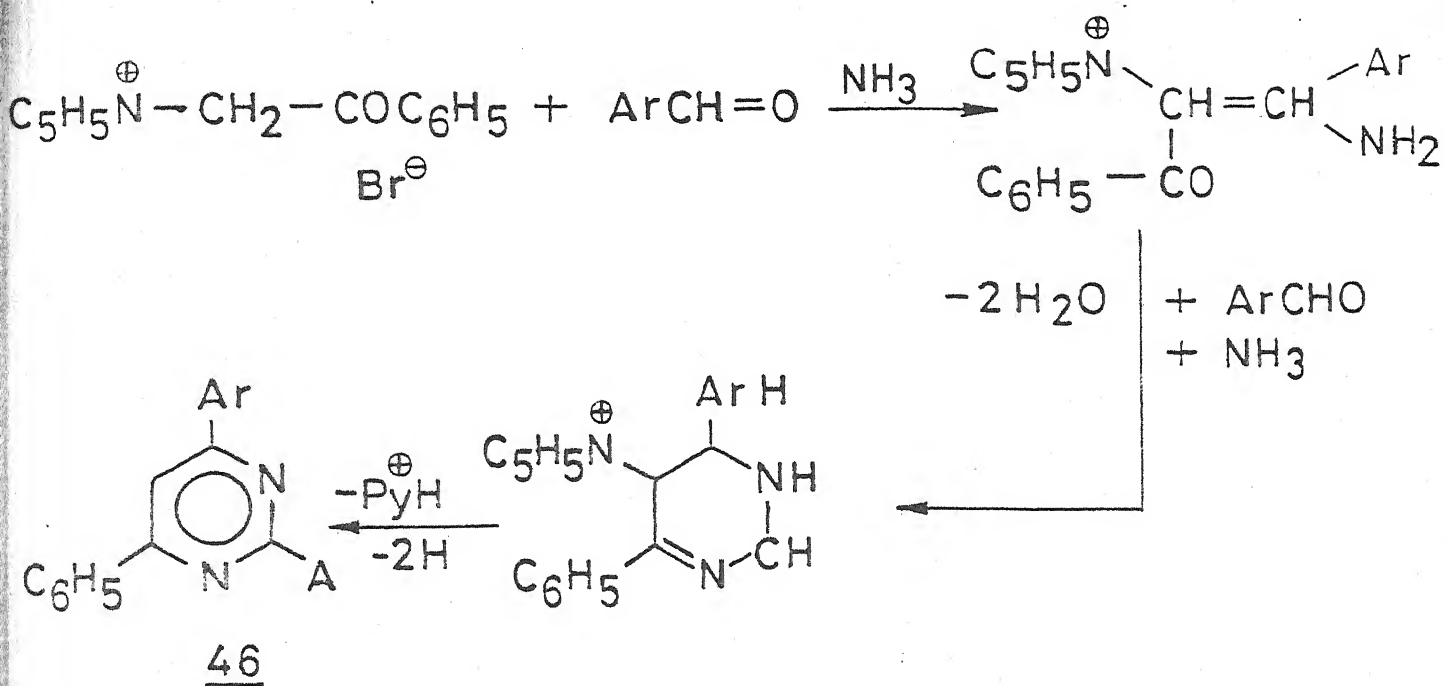
condensation to form the pyridinium salt (42) (Scheme I.21). The pyridinium ylides prepared from the pyridinium salts, (43) having strong electron withdrawing substituents, react with aromatic aldehydes in presence of pyridine to produce vinylpyridinium salts⁵⁹ (44) (Scheme I.22). But the aromatic aldehydes bonded with electron donating groups react with acylmethylenepyridinium ylides (28) at boiling temperature in presence of acetic anhydride to yield vinyl pyridinium salts (45) (Scheme I.23).

In presence of glacial acetic acid, phenacylpyridinium bromide reacts with aromatic aldehydes bonded to substituent with - I effect to form 2,4,6 - triarylpyridines (46) through Mannich type of reaction⁵⁹ (Scheme I.24).

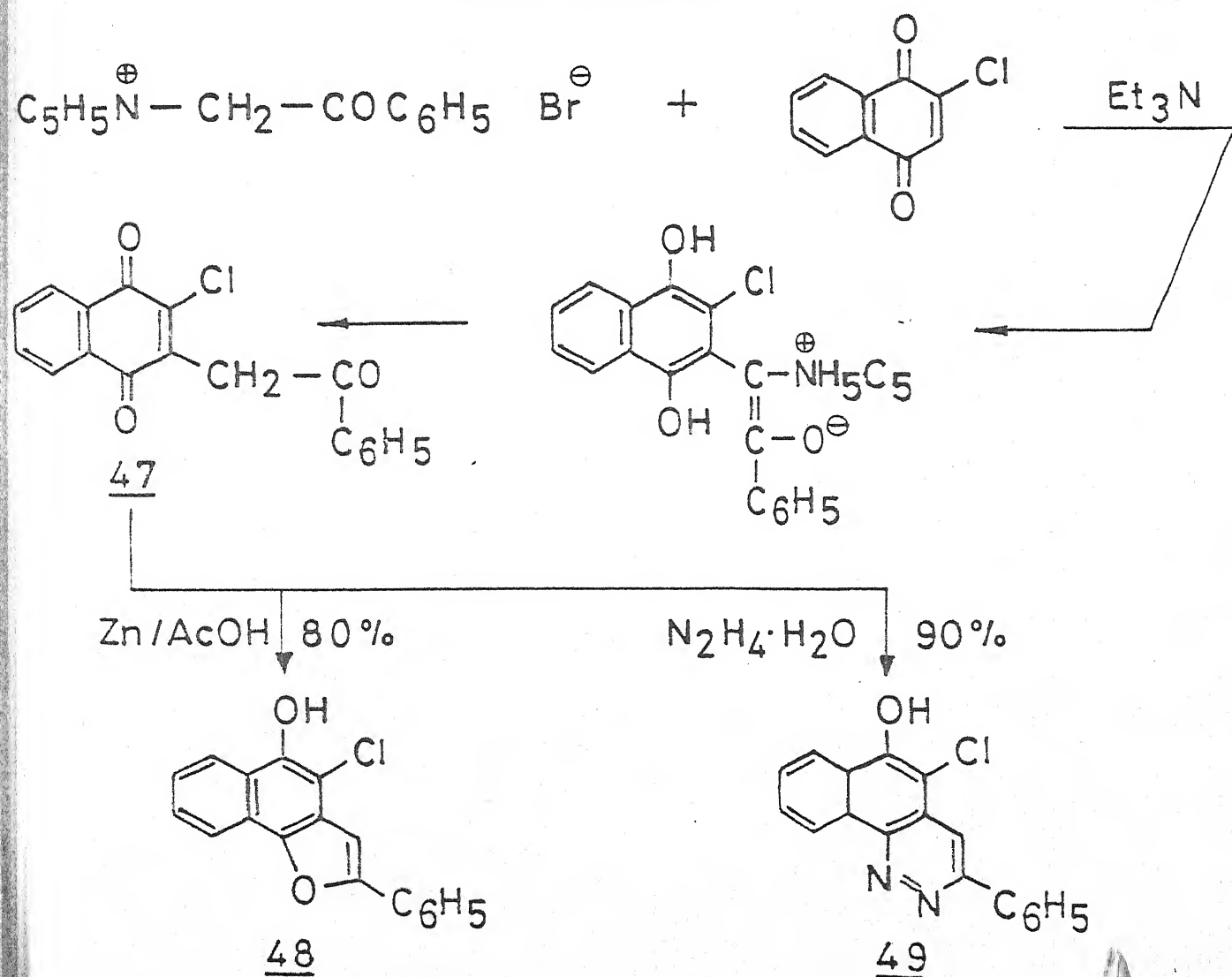
ii. Reaction with ketones : 2 - Chloro - 1 - 4 - naphthoquinone reacts with phenacylpyridinium bromide, following Michael addition, to form a stable substituted phenacylnaphthoquinone (47) which itself undergoes cyclisation to form benzocoumarin (48) in presence of Zinc and acetic acid. With hydrazine hydrate, (47) forms benzocinnoline^{60,61} (Scheme I.25).

The reaction of the non-stabilized ylides with ketones produced aldol type of products (50) (Scheme I.26). But the carbonyl stabilized pyridinium ylides react with tropone to form 3 - phenacyl - 2H - Cyclohepta (b) furan (51)⁶²

Scheme I-24



Scheme I-25



//14//

(Scheme I.27).

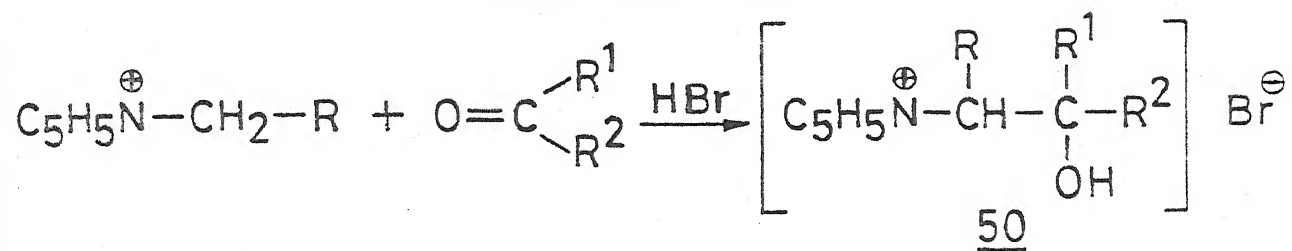
iii. Reactions with α, β -unsaturated ketones : There are a variety of ways in which such ketones can react with pyridinium salts to yield different products. The experimental conditions as well as the nature of substituents attached to the ylide carbanion determine the products formed.

Thus, acylmethylenepyridinium ylides (52) readily attack the α, β -unsaturated carbonyl compounds to undergo Michael addition to form pentane - 1,5 dionypyridinium derivatives (53). The product (53) on treatment with a mixture of glacial acetic acid and ammonium acetate cyclises to yield 2,4,6 - trisubstituted pyridines (54)^{63,64} (Scheme I.28). But N - (aminoformylmethylene) - pyridinium ylides undergo Michael addition with Mannich bases or α, β -unsaturated ketones to form 2 - pyridines (55-56)^{65,66} (Scheme I.29).

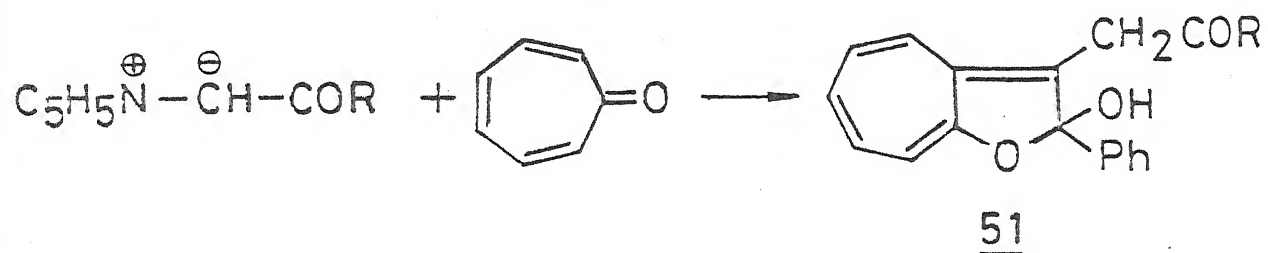
Benzylpyridinium bromide reacts with benzalacetophenone to form 1,3 - diphenylnaphthalenes (58) (Scheme I.30)⁶⁷. Recently, Tiwari⁶⁸ et al have used this reaction in the synthesis of a wide variety of naphthalenes.

iv. Reaction with nitroso compounds : It was first observed by Krohnke and Borner⁶⁹

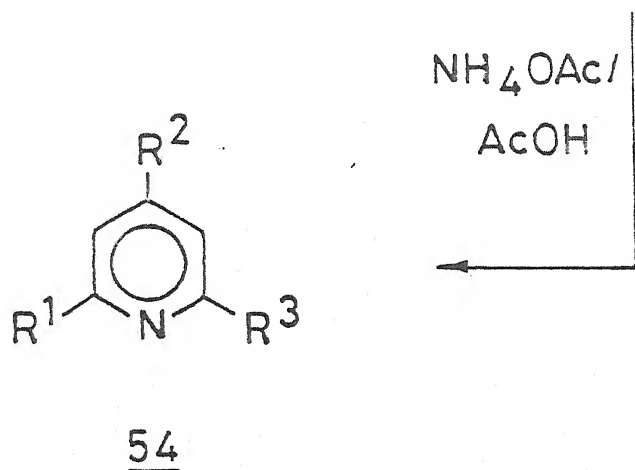
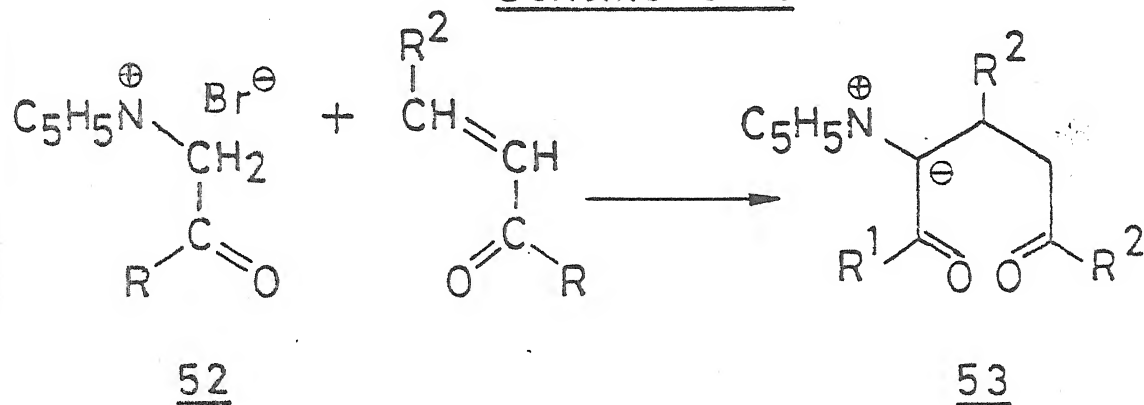
Scheme I-26



Scheme I-27



Scheme I-28



that the ylide generated from N - phenacylpyridinium salt reacts with nitrosobenzene to afford nitron (59) (Scheme I.31). However, the elimination & addition reactions of 4 - bromo - phenacylpyridinium ylides (60) with α -nitro- β -naphthols and α -nitroso- β -naphthylamine lead to the formation of naphthoxazole derivatives (61) and benzoquinoxaline-N-oxide derivatives⁷⁰ (62) respectively (Scheme I.32).

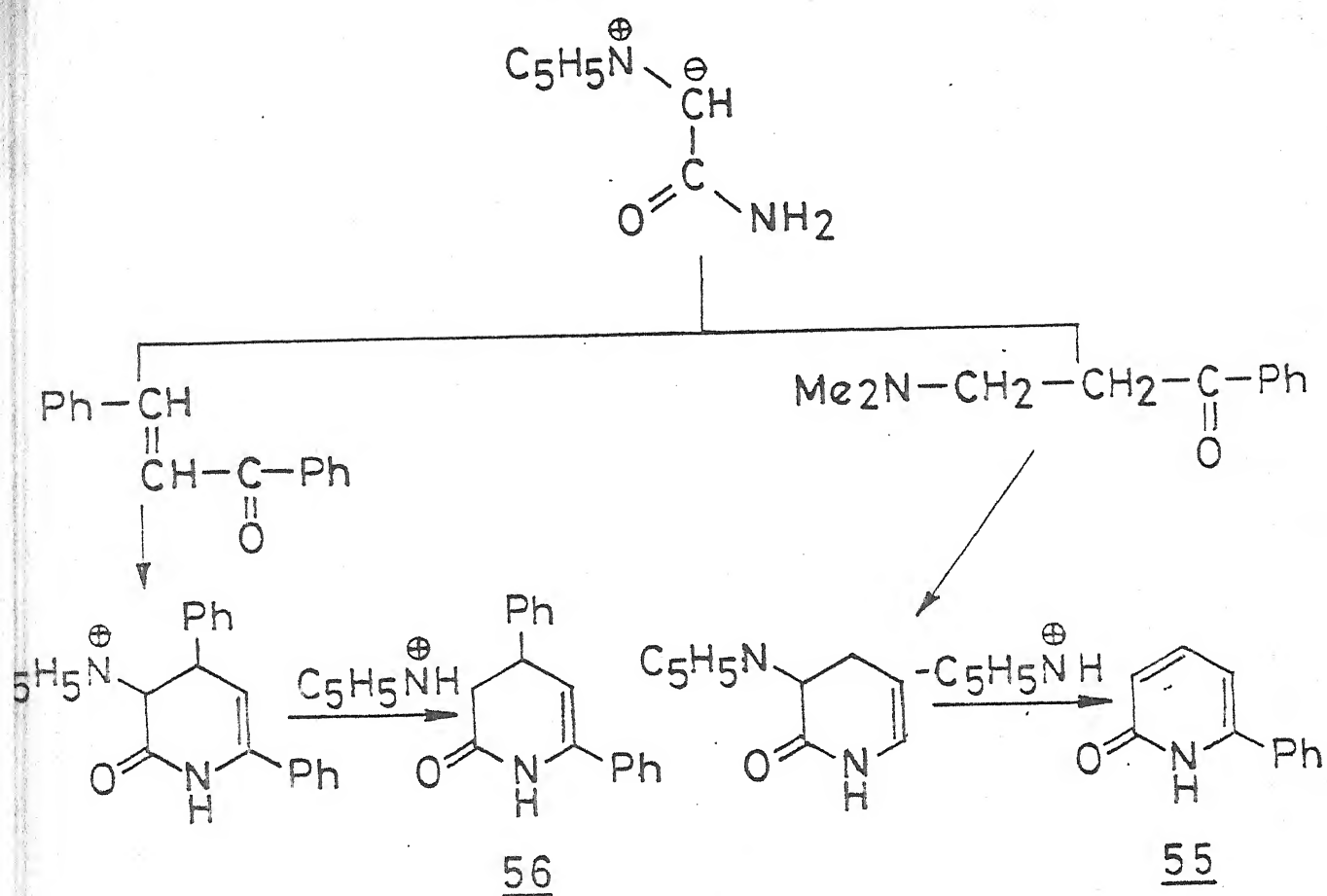
v. Reactions with isocyanates and isothiocyanates: The reaction of N - benzolmethylenepyridinium ylides with phenyl-isocyanate (63a) and isothiocyanate (63b) gives 2 - (α - phenylcarbamoylphenacyl) pyridinium betaine⁷⁰ (64) and 2 - (α - phenylthiocarbamoylphenacyl) pyridinium betaine (65) (Scheme I.83).

vi. Reaction with carbon-sulfur bond : Phenacylpyridinium ylides react with carbon disulfide to give sulphur containing betaine (66). The product yields α - alkylated products⁷⁰⁻⁷¹ (67) on treatment with alkyl halide (Scheme I.34).

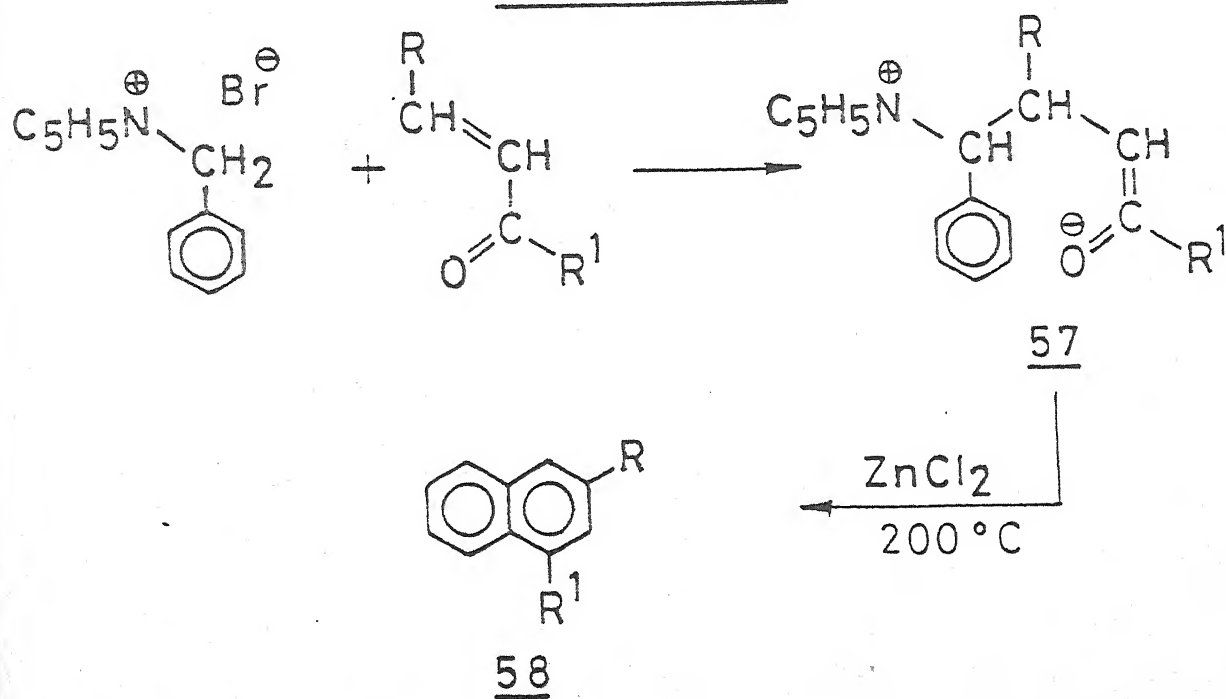
(e) 1,3 Cycloaddition reactions :

On account of delocalization of positive charge over the pyridine ring, pyridinium ylides form 1,3 dipolar systems and can react with dipolarophiles such as acetylenic

Scheme I-29



Scheme I-30



system to form (3 + 2) cycloadducts. This cycloadduct, on dehydrogenation with palladium and charcoal, gives indolizine derivatives⁷²⁻⁷⁷ (68) (Scheme I.35).

(f) Reaction with aromatic amines :

N - phenacylpyridinium ylides react with aromatic amines or o -, p -toluidines to afford substituted indoles⁷⁸⁻⁷⁹ (Scheme I.36). But the reaction of the pyridinium ylide with o - phenyldiamine in boiling acetic acid gives 2 -phenyl-benzimidazole⁶³ (70) (Scheme I.37).

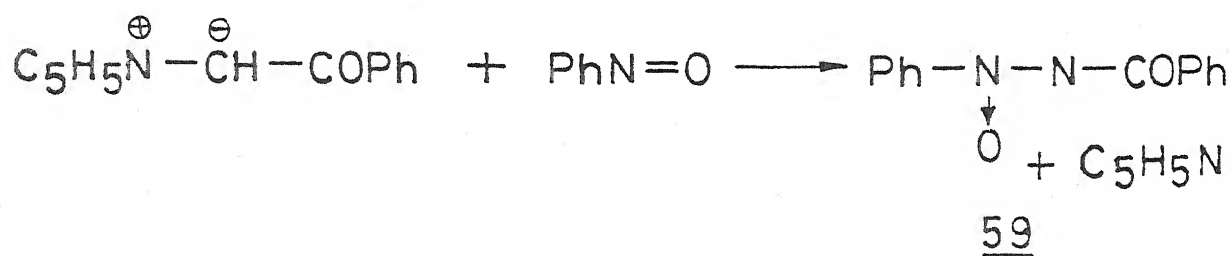
(g) Reduction :

Ketones (71) and diketones^{35,72} (72) are formed when alkylated and acylated phenacylpyridinium ylides are reduced with zinc and acetic acid (Scheme I.38).

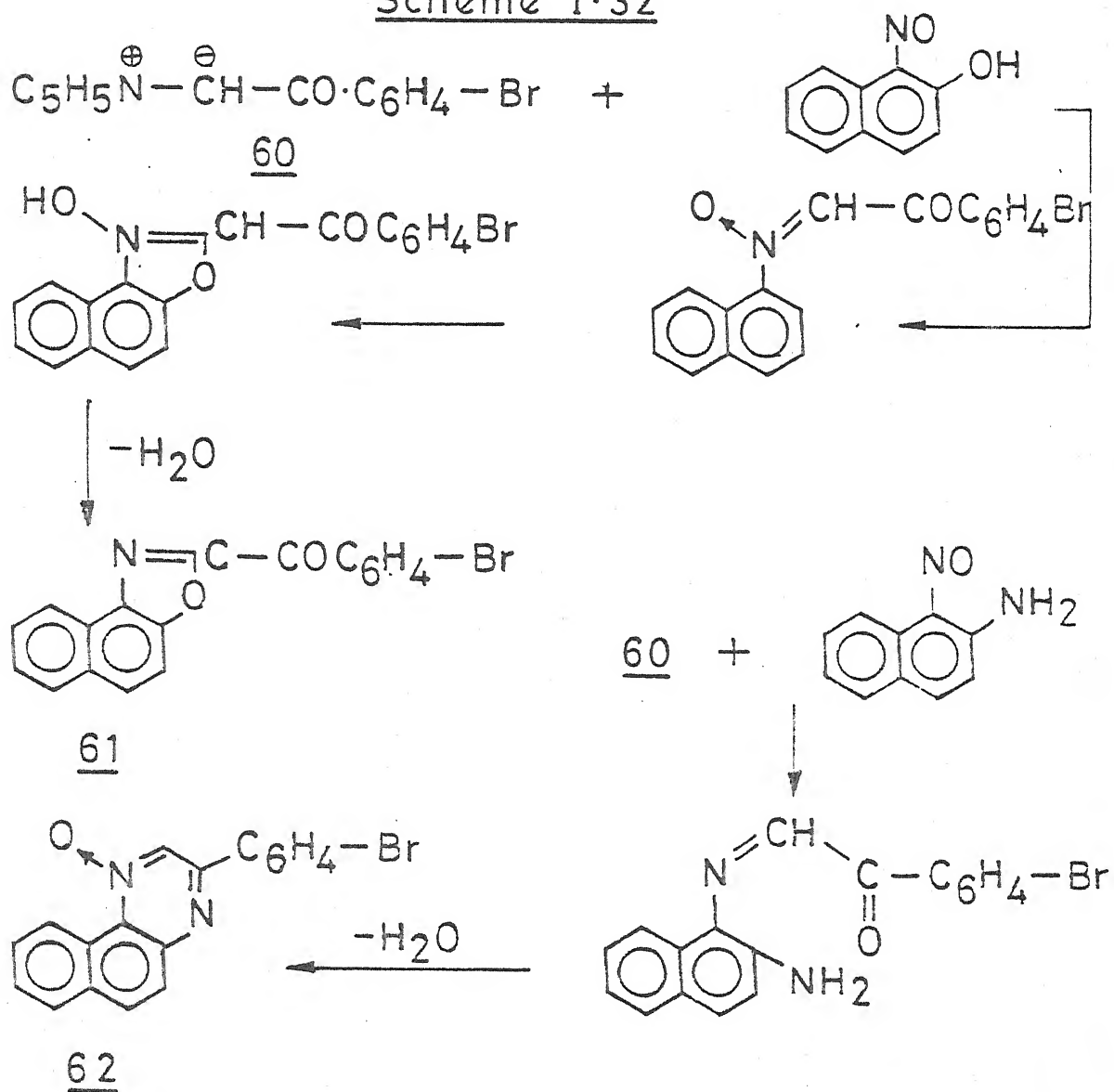
(h) Thermolysis :

Little information is available about the thermal stability of pyridinium ylides. The pyridinium ylides when heated above their melting points & under reduced pressure decompose into dibenzoylethylene⁶⁵ (74) (Scheme I.39). But the thermolysis of the ylides in benzene in presence of Copper or copper oxide gave the unexpected product 1, 3 dibenzoylindolizine^{72,80} (75) (Scheme I.39).

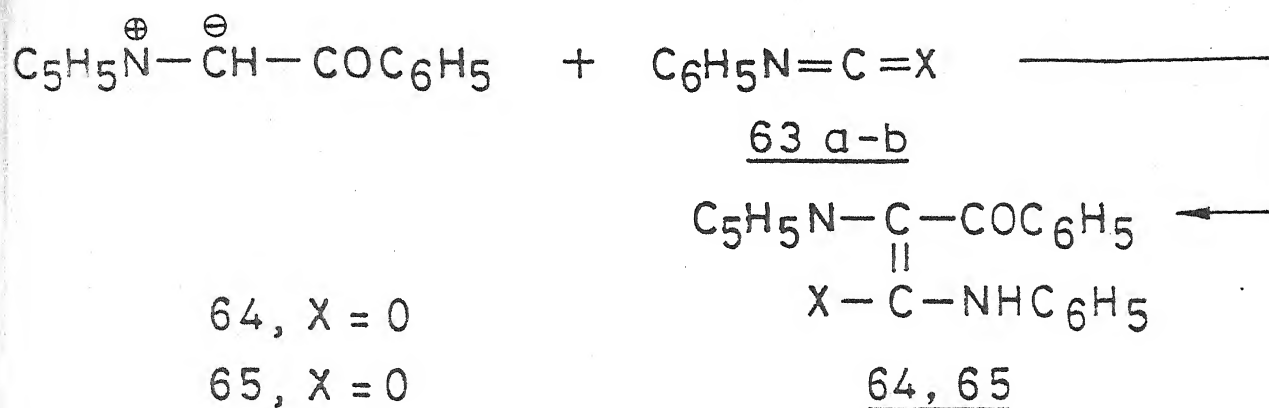
Scheme I-31



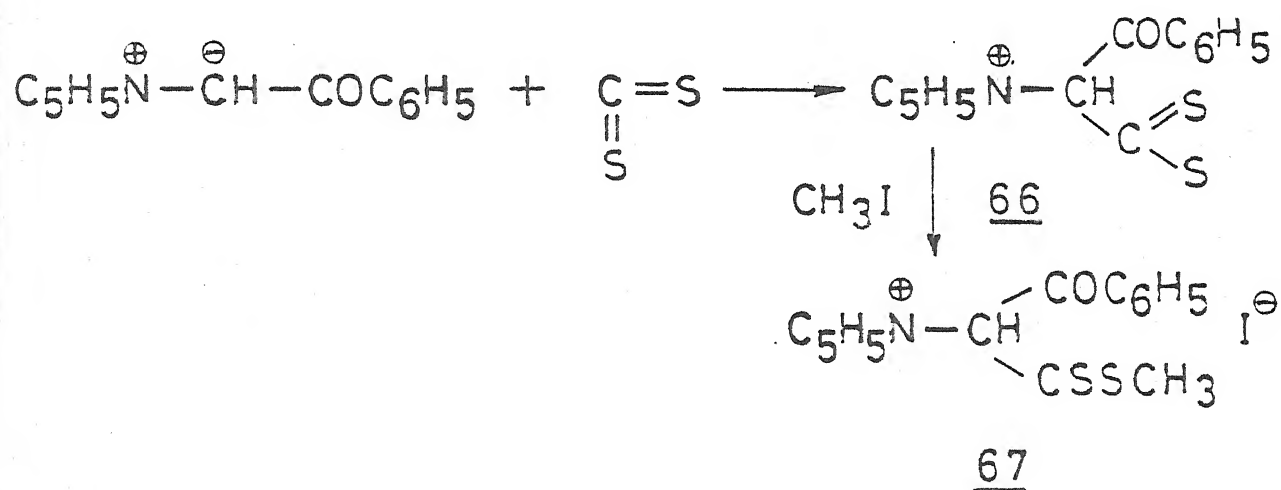
Scheme I-32



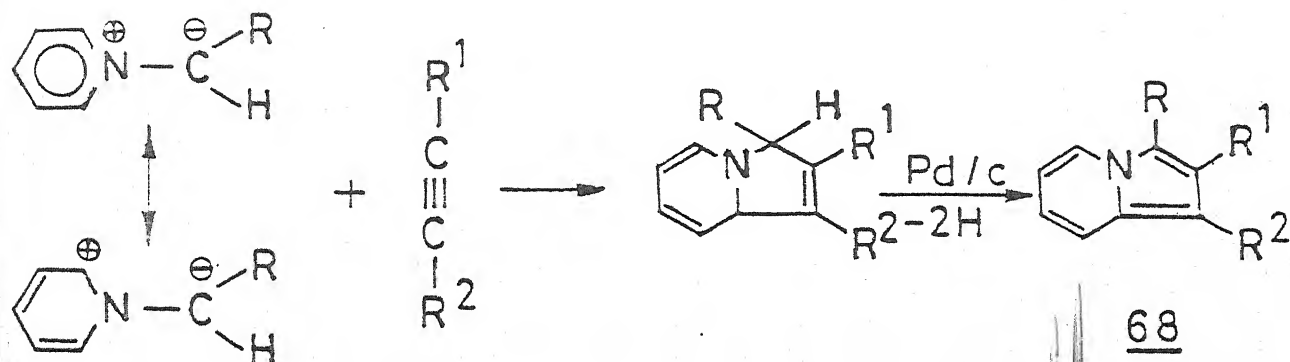
Scheme I.33



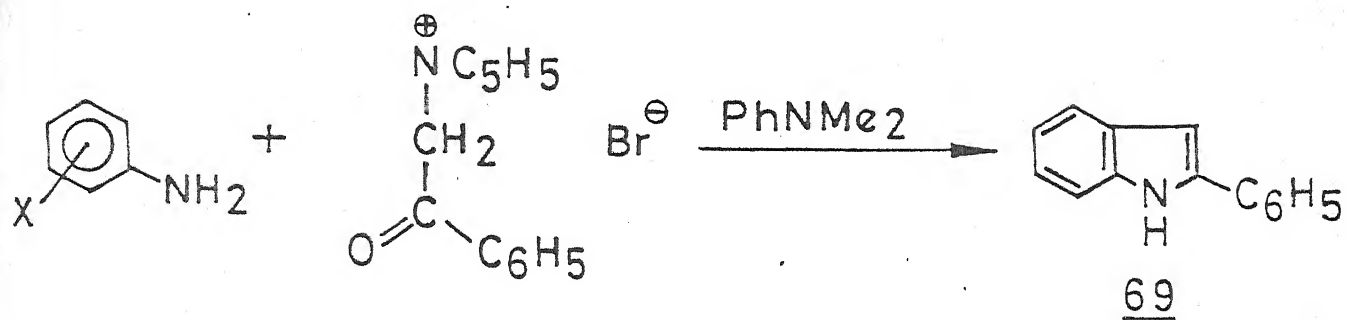
Scheme I.34



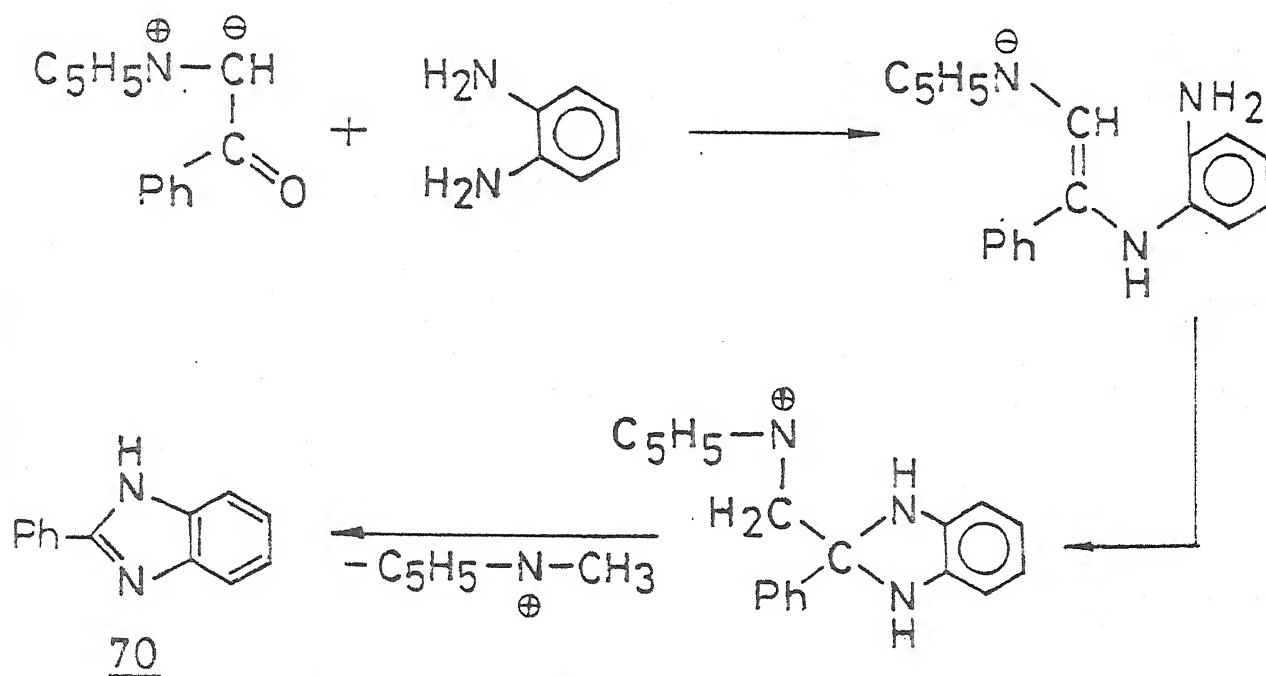
Scheme I.35



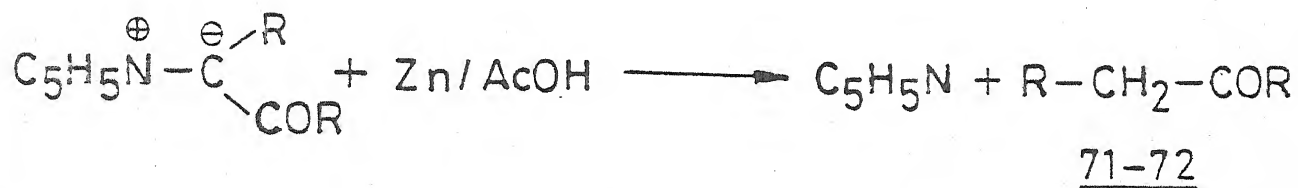
Scheme I-36



Scheme I-37



Scheme I-38



71, R = Alkyl

72, R = Aroyl

(i) Photolysis :

There is dearth of literature in this field too. Streith et al⁸¹ isolated a pyrrole derivative (77) and dicyanonorcarbadiene (78) by irradiating pyridinium-dicyanomethylide (Scheme I.40). The product (78) was supposed to be formed by the attack of dicyanocarbene intermediate (76) on benzene.

(j) Reaction with aryldiazonium salts :

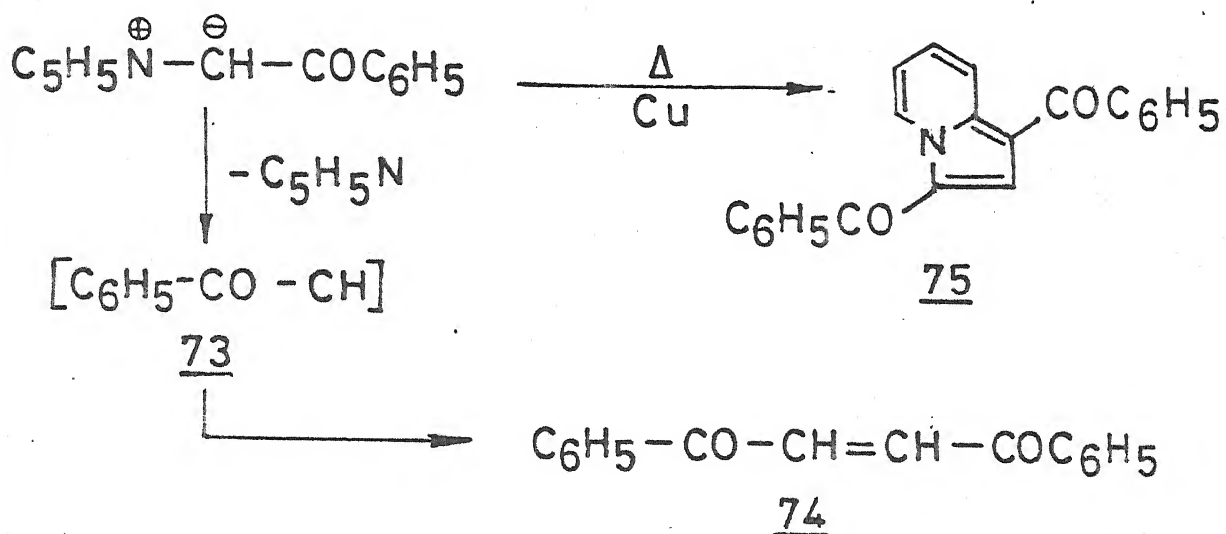
Recently, Bansal et al⁸² have developed a new route for the synthesis of 1,4 - dihydro - 1,2,4,5 - tetrazines by the reaction of phenacylpyridinium ylides(79) with aryldiazonium salts in presence of cold solution of sodium acetate (Scheme I.41).

1.3 PHOSPHONIUM YLIDES :

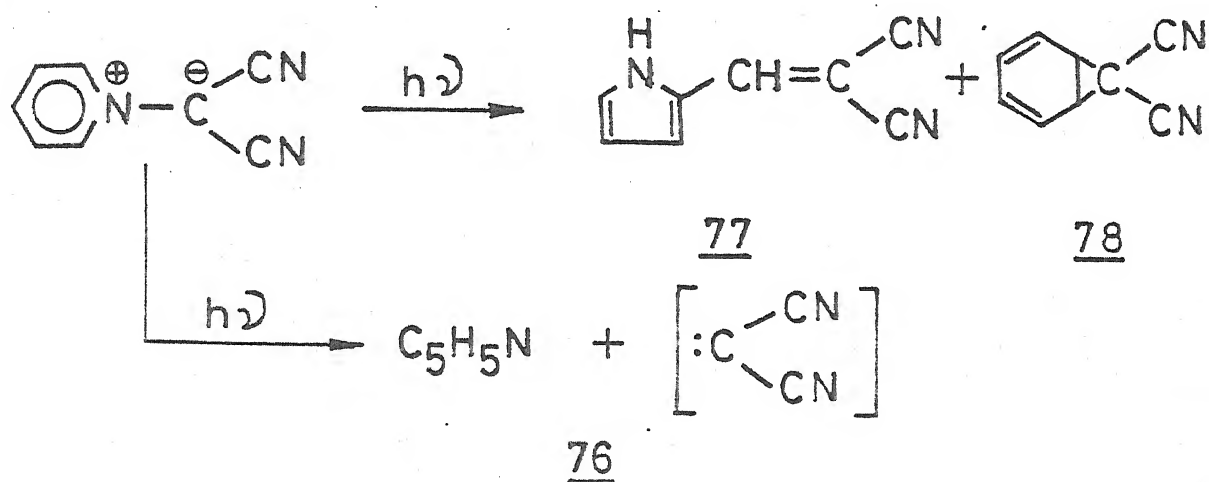
1.3.1 GENERAL REMARKS :

In the late forties, Wittig⁸³ concentrated his attention towards pentavalent compounds of nitrogen and discovered the nitrogen ylide of the type (82). As a natural corollary, he extended his investigations to the next higher element i.e. phosphorus of the V group. In his first attempt to prepare the isomers of pentaphenyl phosphorus compounds lead to the first ever synthesis of crystalline

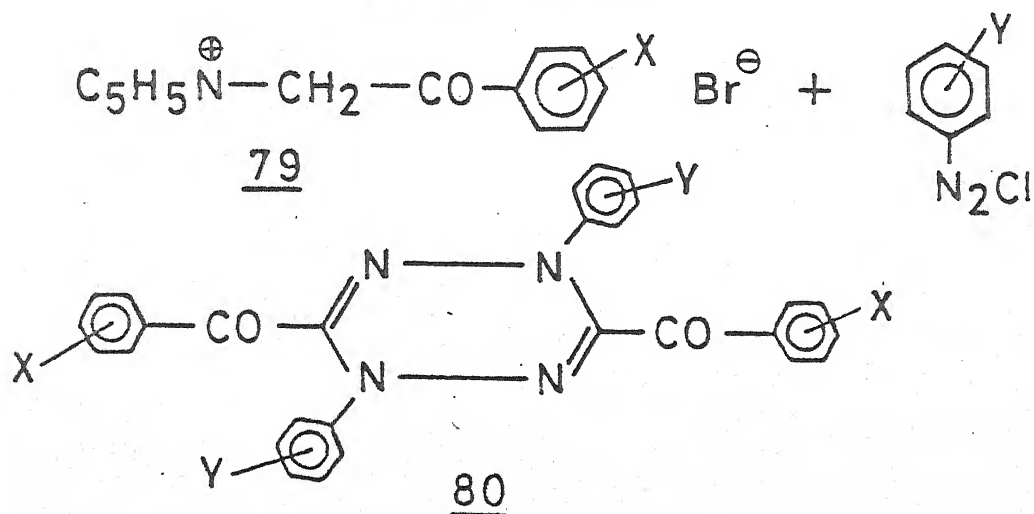
Scheme I-39



Scheme I-40



Scheme I-41



methylenetriphenylphosphorane (85). Wittig et al⁸⁴ observed that the product (85) reacted with benzophenone (83) to give an almost quantitative yield of 1, 1-diphenylethylene (86) and triphenylphosphine oxide (Scheme I.42).

The stability of the phosphorus ylides is mainly due to the possibility of 3d orbitals of phosphorus forming actual π bonds⁸⁵ which can be represented as resonance hybrids of two limiting structures (87a) and (87b). This explains why comparatively greater number of phosphorus ylides have been isolated and characterised as stable species.⁸⁶⁻⁹⁵

The phosphonium ylides may be classified into two main groups on the basis of their reactivity. The first and the bigger group consists of alkylidenephosphoranes which have low stability and hence high reactivity. The second but smaller group includes highly stable unreactive resonance stabilized phosphoranes.

Basically, the phosphonium ylides can undergo two main types of reactions: the ones in which the ylide carbanion is mechanistically involved and the ones in which both the ylide carbanion and the heteroatom participate.

The distribution of negative charge in the molecule which is dependent upon the nature of substituents

R^1 and R^2 in the alkylidene portion as well on the group R on phosphorus determines the reactivity of alkylidene phosphoranes. Thus, if the lone pair of electrons on the α -carbon atom of the ylide form (87a) is delocalized over the R^1 and R^2 groups, the nucleophilic nature of phosphoranes is diminished and the stability enhanced. The electron withdrawing substituents R^1 and R^2 stabilize the negative charge and hence reduce the reactivity of these ylides. However, in the absence of any such interaction, an extremely reactive and stable ylide is expected to be formed.

1.3.2 GENERATION OF PHOSPHONIUM YLIDES :

(a) Ylides from phosphonium salts :

The most common method for the generation of phosphonium ylides⁸⁶ involves the action of suitable bases on quaternary phosphonium salts (88)(Scheme I.43). A non-polar solvent such as benzene is usually chosen as the medium of reaction. But some times a more polar solvent may have to be used. The strength of the base required for deprotonation of phosphonium salts depends upon the acidity of the latter and more specifically on the substituents R^1 and R^2 on the ylide carbanion. Such bases may be ammonia⁹⁶, triethylamine,^{97,98} pyridine,^{98,99} sodium hydroxide,⁹⁶⁻¹⁰¹ sodium methoxide,¹⁰² sodamide,¹⁰³ sodium

//20//

hydride,¹⁰⁶ potassium ter-butoxide,¹⁰⁴ lithium piperidine,¹⁰³
butyl lithium¹⁰⁶ and phenyl lithium.¹⁰⁷

(b) From carbenes and triphenylphosphine :

It is possible to prepare phosphonium ylides by the reaction of carbon tetrachloride or bromide with triphenylphosphine^{108,109} (90) (Scheme I.44). The diazoalkyl phosphates (91) can also serve as source for carbenes for the preparation of phosphonium ylides (92) provided they are decomposed in presence of Cu (I) salt. It is because generally triphenylphosphine reacts with diazo compounds to form phosphazine¹¹⁰ (93) (Scheme I.45).

(c) Other methods:

The chemical literature contains a large number of methods for the preparation of phosphonium ylides. Thus, the reaction of triarylphosphine with a compound having an activated double bond^{108,111,112} (Scheme I.46), pyrolysis of phosphonium salts¹¹³ (96) (Scheme I.47), action of phenyl lithium on vinyltriphenylphosphonium bromide¹¹⁴ (97) (Scheme I.48), reaction of dihalotriphenylphosphine (99) on active methylene compounds¹¹⁵ (100) (Scheme I.49) etc. are some of the reactions.

There is only one example¹¹⁶ of ylide (104) preparation using benzyne intermediate (102) with tertiary

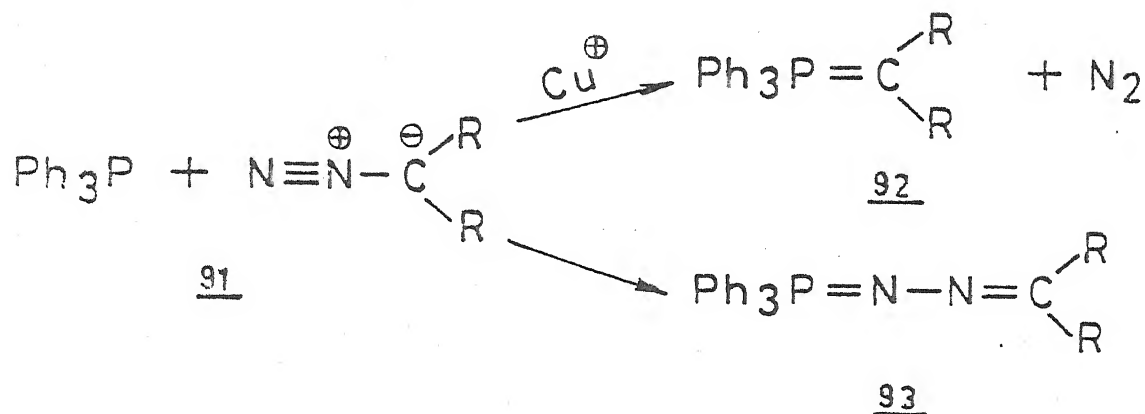
Scheme 1.44



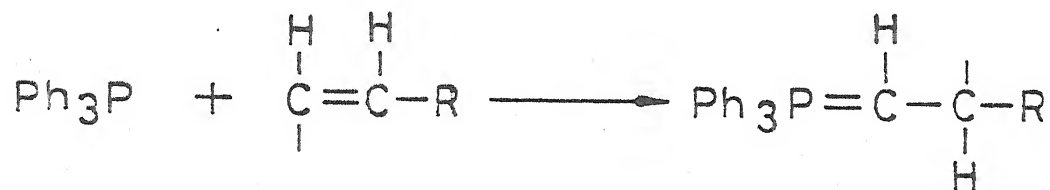
90

X = Cl, Br

Scheme 1.45

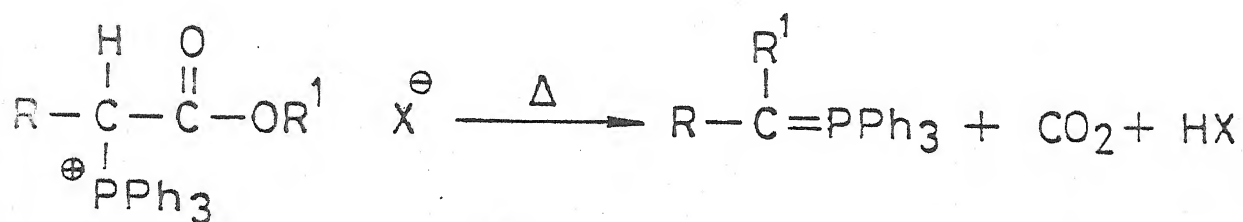


Scheme 1.46



R = COOR¹, CONH₂, CN etc. 94

Scheme 1.47



95

96

phosphine (Scheme I.50). Synthesis of ylides can also be brought about by the reaction of triphenyl phosphine with reactive triflates (105) to yield phosphonium salts (106) which when treated with the base DBU yield ylides¹¹⁷ (107) (Scheme I.51).

Stable ylides are obtained from unstable ylides (108) by their reaction with alkyl halides¹¹⁸ or acyl halides.¹¹⁹ The process may be designated as tranxylation since two molecules of the unstable ylide (108) react with the halide to form a new carbonyl stabilized ylide (110) (Scheme I.52).

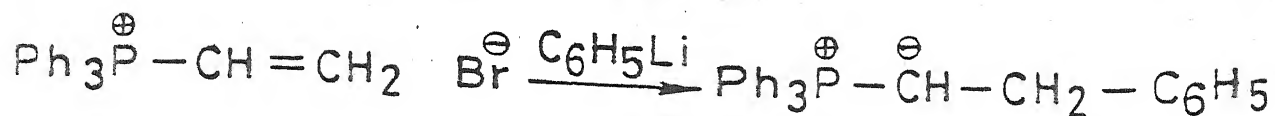
1.3.3. REACTIONS OF PHOSPHONIUM YLIDES :

Phosphonium ylides, derived from their precursor phosphonium salts by dehydrohalogenation, are attacked by hydrogen halides to regenerate the original salt. Hence phosphonium salts may be considered as Bronsted acids and the phosphonium ylides as Bronsted bases (Scheme I.53).

(A) Oxidation :

Oxidation of phosphonium ylides (111) involves the breakup of the carbon-phosphorus bond to form a carbonyl compound (112) which further reacts with the starting ylide (111) to give an olefin (113) and phosphine oxide¹²⁰⁻¹²¹ (Scheme I.54).

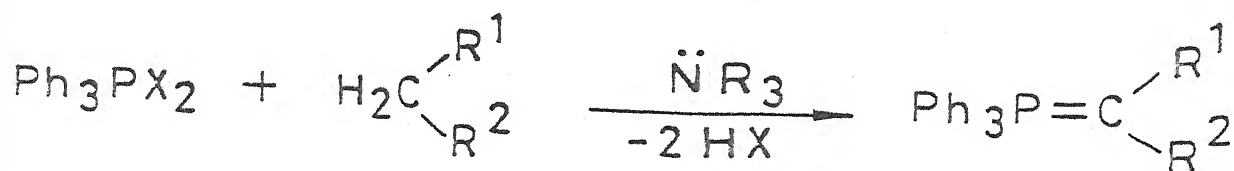
Scheme I.48



97

98

Scheme I.49

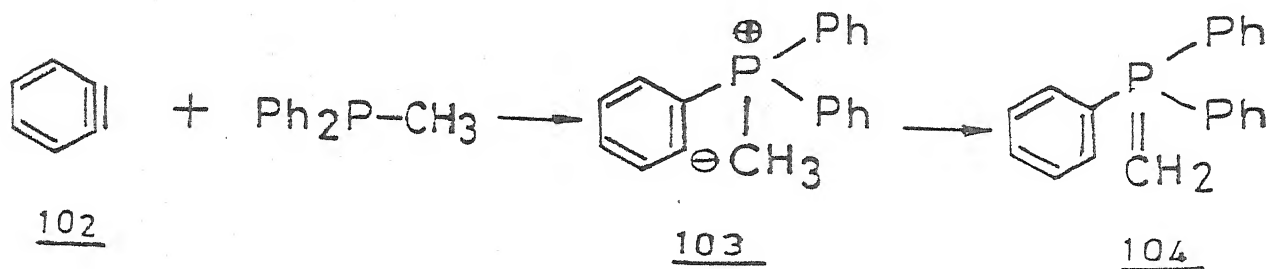


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100

101

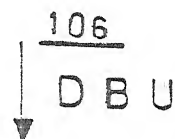
Scheme I.50



Scheme I.51

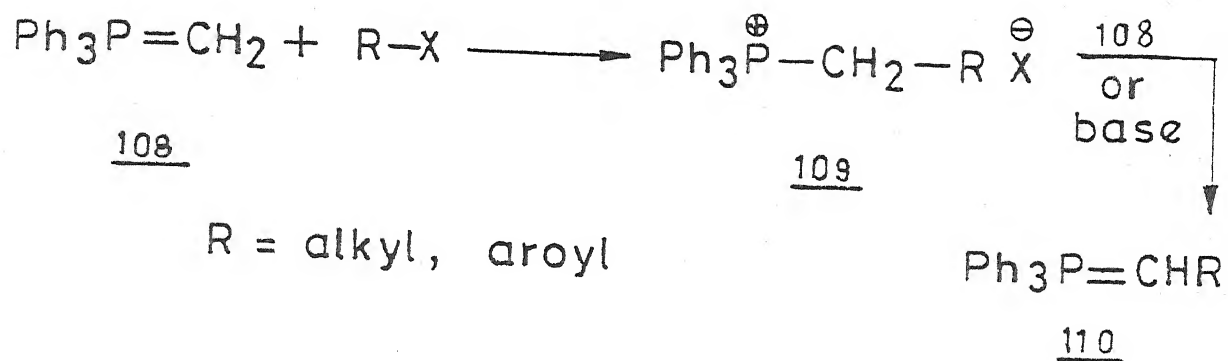


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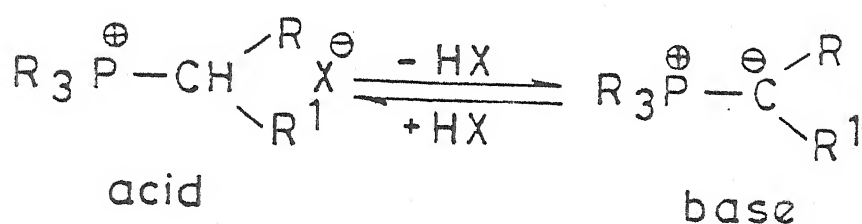


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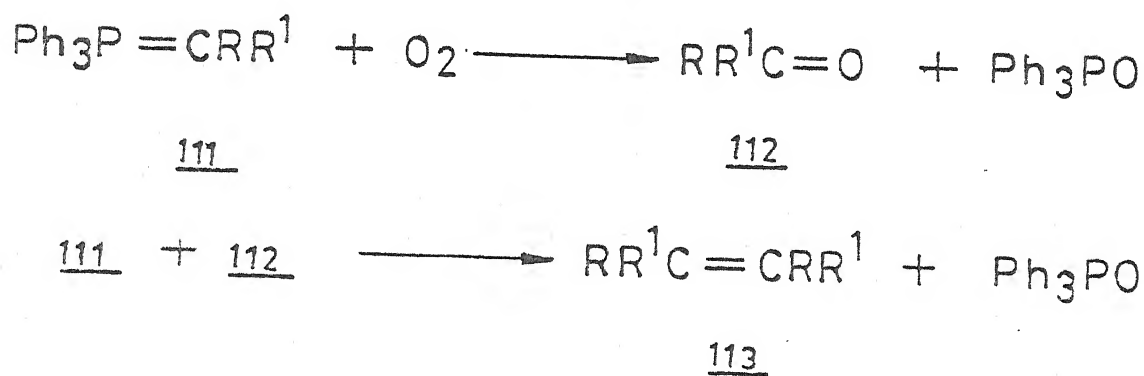
Scheme I-52



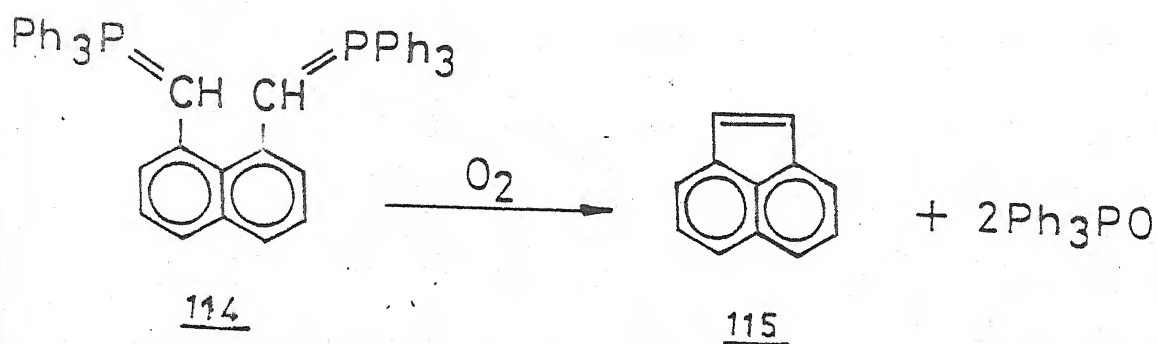
Scheme I-53



Scheme I-54



Scheme I-55



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In the case of bis ylides (114), the autooxidation reaction leads to the formation of olefins, acenaphthylene (115) (Scheme I.55) and heterocyclic olefins¹²² (117) (Scheme I.56).

Important oxidising agents used for the oxidation of ylides are ethylnitrate, lead tetraacetate, dibenzoylperoxide, phenyliodide diacetate and lead dioxide¹²⁴. Oxidation with ozone¹²⁵ and periodate¹²⁶ is more useful in the synthesis of dicarboxy compounds.

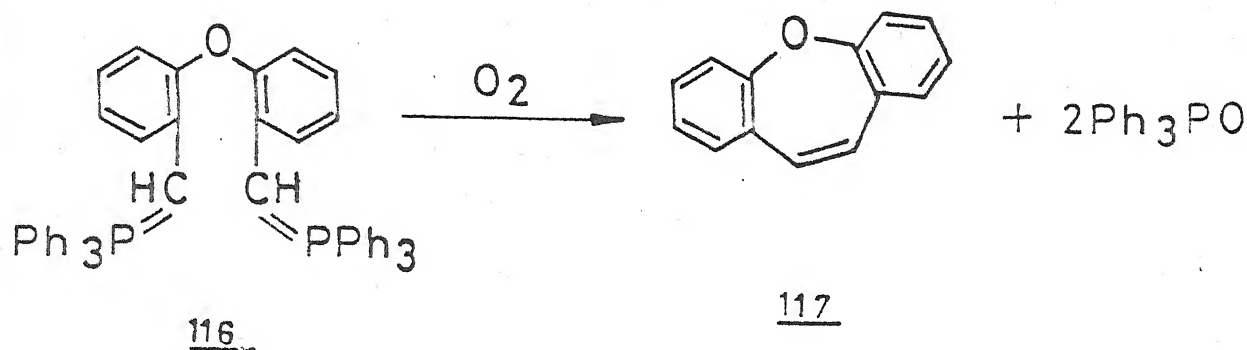
(B) Alkylation and acylation :

The alkylation of the phosphonium ylides (118) with alkyl halides leads to phosphonium salts (119) which on reaction with another mole of the original ylide (118) give alkyl substituted ylides¹²⁷ (120) alongwith salt (121) (Scheme I.57). But the carbonyl stabilized ylides (122) undergo C - alkylation as well as O - alkylation because of mesomeric forms of ylides¹²⁸ (122) (Scheme I.58).

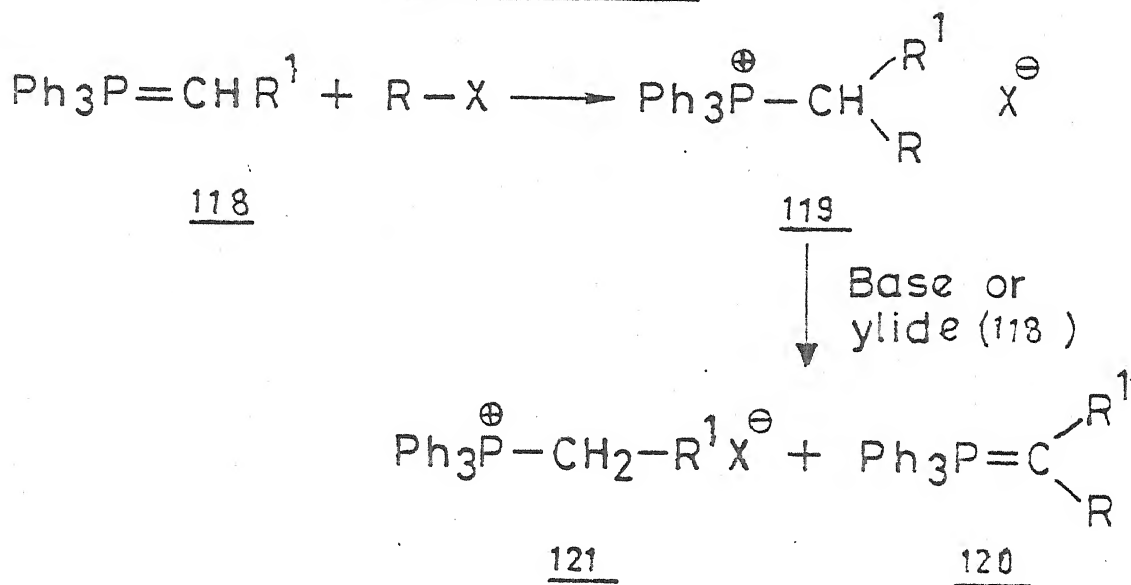
It is also possible for alkylation to occur intramolecularly if the ylide contains a halogen in the long chain to form cyclic products^{129,130} (125) (Scheme I.59).

The acylation of ylide (126) may be carried out with an acid chloride to yield an acylated phosphonium salt which then undergoes transylidation reaction with another

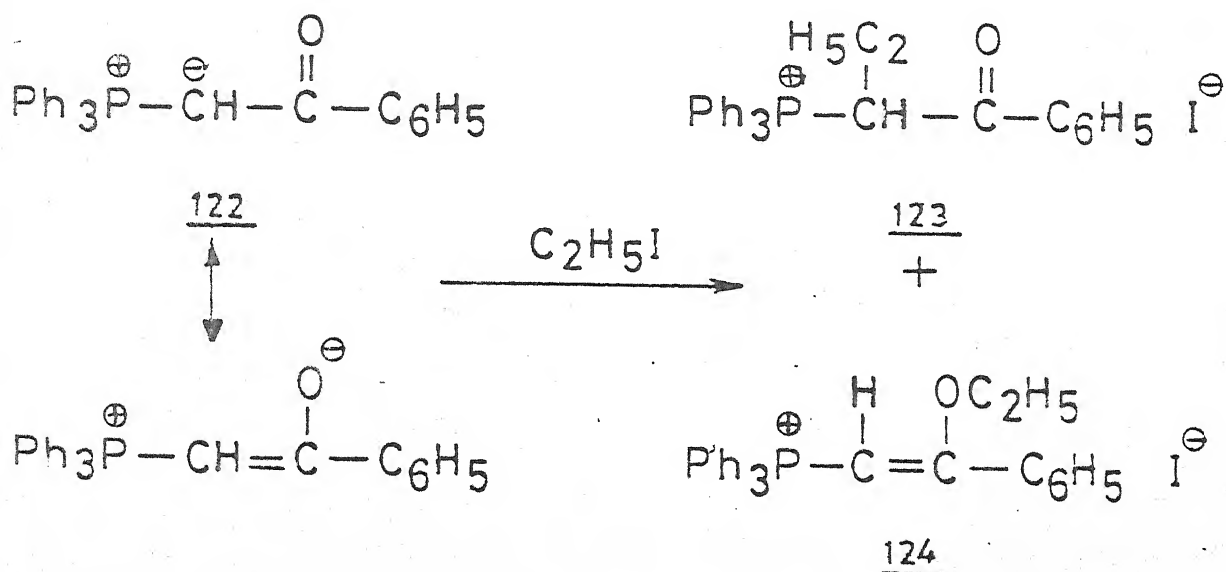
Scheme I-56



Scheme I-57



Scheme I-58



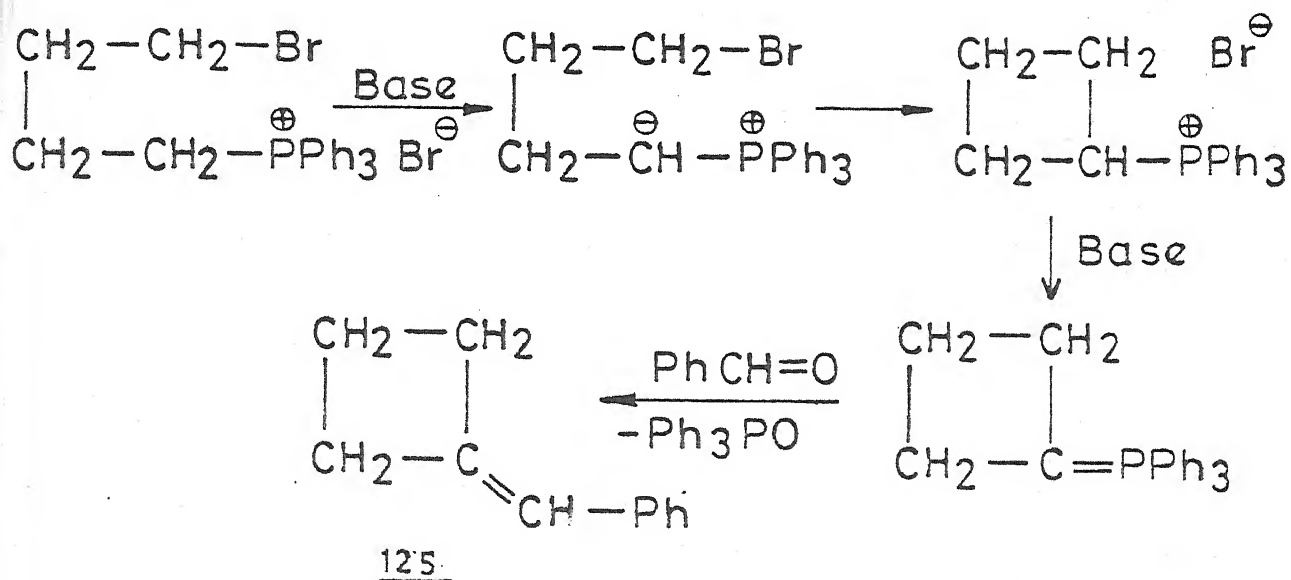
mole of the ylide (126) to form the acylated ylide¹³¹ (128) (Scheme I.60). Acid esters,^{98,132} Chloroformic acid ester,¹³¹ acid anhydride,¹⁴³ thiocarbonic acid & δ -ethyl esters¹³² may also be used as acylating agents.

Tewari et al¹³⁴ have investigated the transylation of semi-stabilized phosphonium ylides to give highly stabilized ylides. Yoshida et al¹³⁵ have reported the reaction of the ylide (129) with imidoyl chloride (130) to form α -iminophosphoniummethyllide (131) through transylation reaction (Scheme I.61). Recently, it has been observed¹³⁶ that β -ketophosphoranes yield O-acetylated products on acylation with acid chlorides.

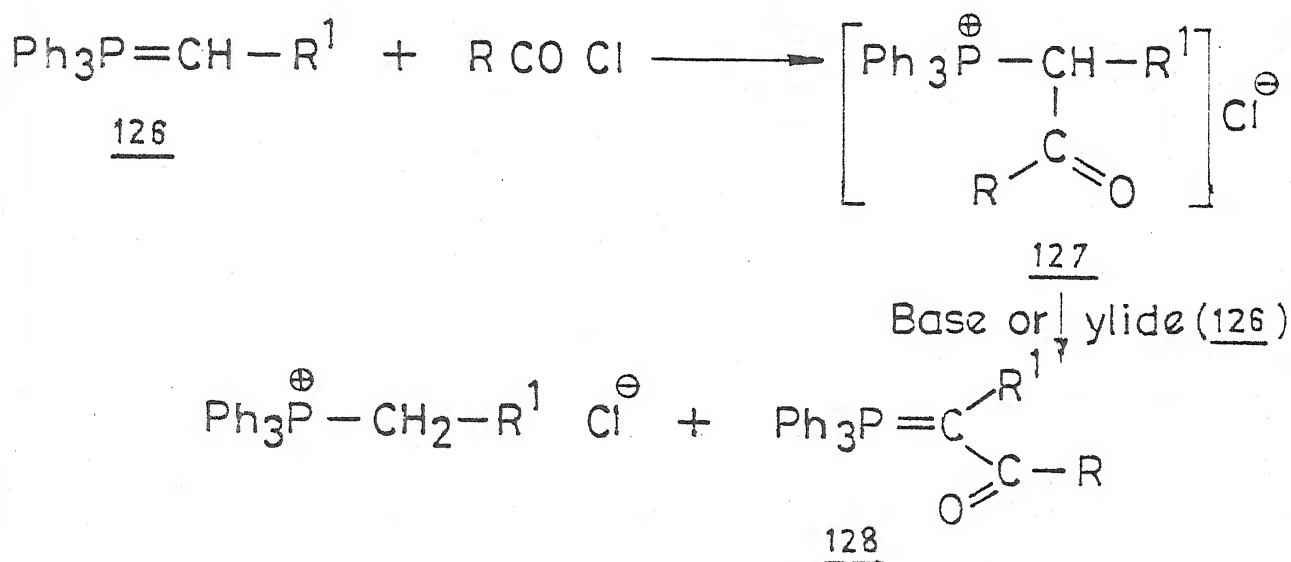
(C) Reaction with multiple bonds :

1. With carbonyl compounds (Wittig Reaction): Wittig reaction is the most important reaction of phosphonium ylides and is increasingly showing growing potential for use in preparative Organic Chemistry. It involves the condensation of the ylides with carbonyl compounds to form olefins and phosphine oxide⁶. During the course of the reaction, betaine type of compounds (134a) appear to form as intermediates by the nucleophilic attack of the ylide carbanion (132) on the carbonyl group (133). The intermediate betaine type of compounds, on decomposition through cyclic transition state (134b), give

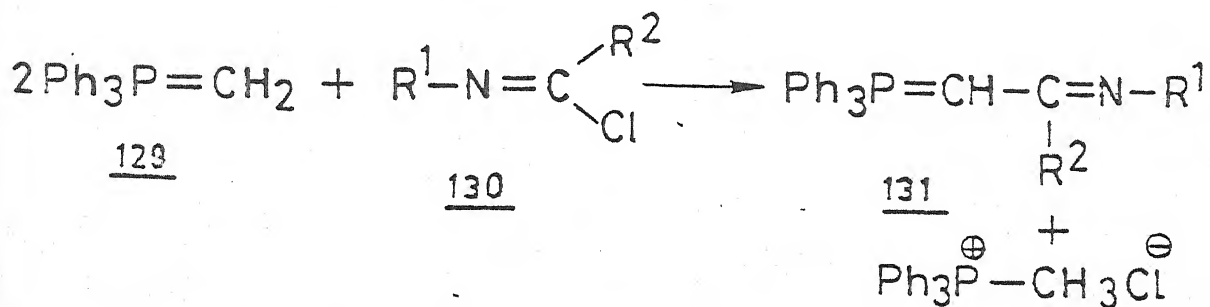
Scheme I-59



Scheme I-60



Scheme I-61



olefins (135) and phosphine oxide^{6,137-39} (Scheme I.62). The overall reaction is made up of two steps and either of the two steps may be the rate determining step.

MECHANISM OF WITTIG REACTION :

I. Betaine formation :

This is the first step of Wittig reaction which involves the nucleophilic addition of the alkylidenephosphorane group to form phosphonium betaine (134a). Consequent upon the great affinity of the phosphorus atom to expand its valence shell to ten electrons, P - O bond is formed.

The ease of formation of betaine intermediate depends upon the nature of the substituents R^1 and R^2 in the alkylidene portion as well of the group R on the phosphorus atom. Electron withdrawing nature of the group R increases the d - orbital resonance to favour the ylide form to decrease the reactivity of the ylide. Electron releasing substituents diminish the formal charge on the phosphorus atom to make greater contribution to the ylide form to increase its reactivity.^{1,2,12} On similar lines, the nucleophilic character of the ylide is diminished if the lone pair of electrons is delocalized into R^1 and R^2 groups. In general, electron withdrawing nature of groups R^1 and R^2 stabilize the negative charge. Obviously,

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therefore, the nucleophilic character of the ylide is diminished. On the other hand, the electron releasing substituents R^1 and R^2 increase the nucleophilicity of the ylide.

II. Betaine decomposition :

In the second step, the decomposition of the betaine to olefin (135) and phosphine oxide takes place by the attack of the oxyanion on phosphorus atom to form a four membered cyclic betaine¹⁴⁰ (134b). Greater affinity of the tertiary phosphine for oxygen provides the driving force for the decomposition of the betaine. This step is retarded by substituents R which decrease the positive character and hence the oxygen affinity of the phosphine (hyperconjugative effect) and accelerated by the substituents R^1 and R^2 which can conjugate with incipient double bond in the transition state. Thus, it is clear how betaine formation is helped and how betaine decomposition is hindered and vice versa.¹³⁹⁻¹⁴¹

STEREOCHEMISTRY OF WITTIG REACTION :

In larger number of cases, the Wittig reaction appears to produce trans olefins as the main product.¹⁴²⁻¹⁴⁷ It has been observed¹⁴⁸ that normally the carbonyl olefination is not stereoselective and both the Cis and trans isomers

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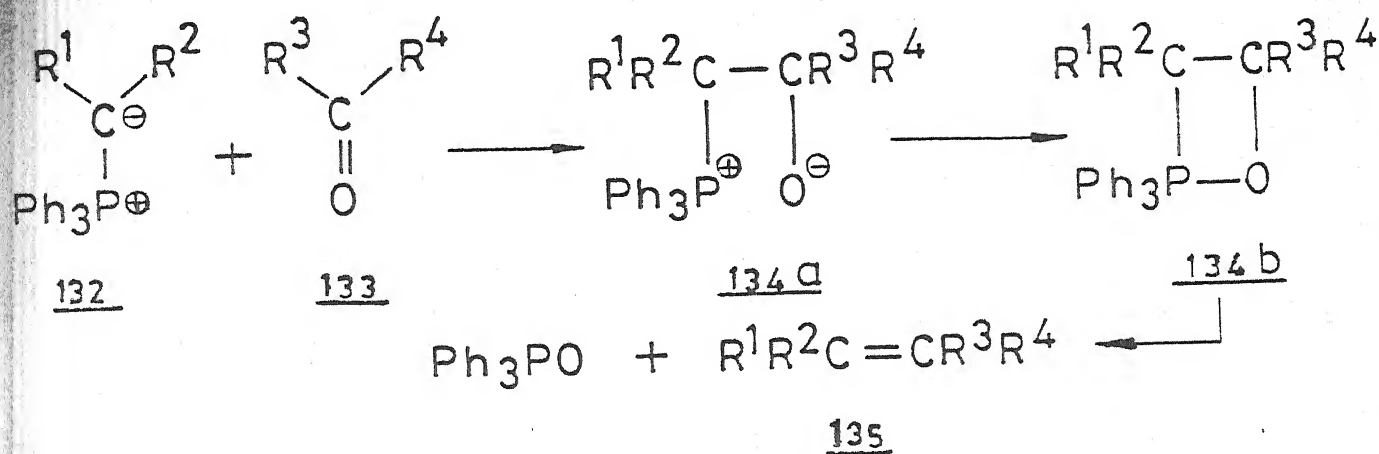
are obtained in comparable amounts. However, a flurry of work in this area has eventually lead to the steric control of olefin synthesis.

On the basis of mechanism of the Wittig reaction discussed above if the ylide and the carbonyl compound are both unsymmetrically substituted, a mixture of Cis and trans isomers is obtained. The ratio of the two products is controlled by a combination of steric factors and reaction conditions.^{1,2,12,149}

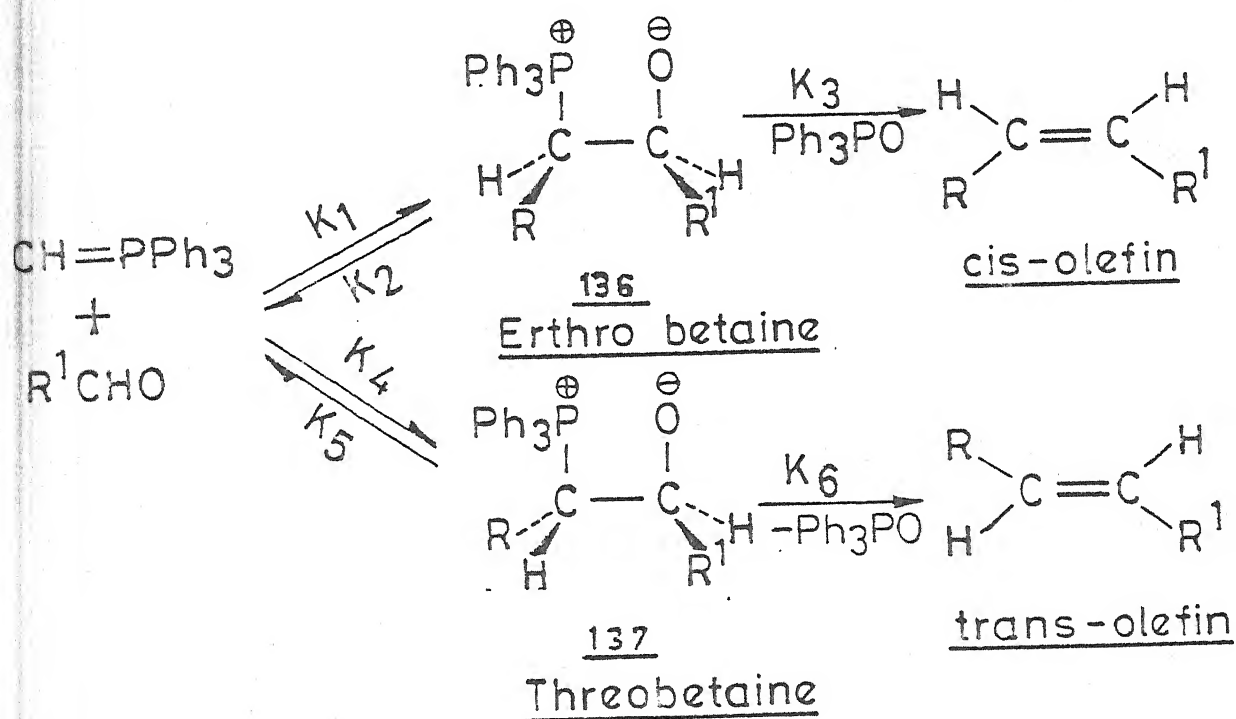
The phosphonium ylide can approach the carbonyl compound to yield a betaine having either erythro (136) or threo (137) configuration (Scheme I.63).

The threo configuration is sterically more favoured and it is expected that the trans isomer (which is thermodynamically more stable) would predominate. It is known that there is no direct conversion of one betaine into the other but only through reversion to the parent ylide and the carbonyl compound.¹⁵⁰ But in presence of phenyllithium the interconversion of the diastereoisomeric betaines (136 & 137) is very rapid with equilibrium as shown in scheme I.63. Addition of HCl followed by potassium-t-butoxide yields pure trans olefins.¹⁵¹ In non-polar solvents, the trans isomer is the major product. Increasing polarity of the solvent increases the amount of the Cis-olefin.

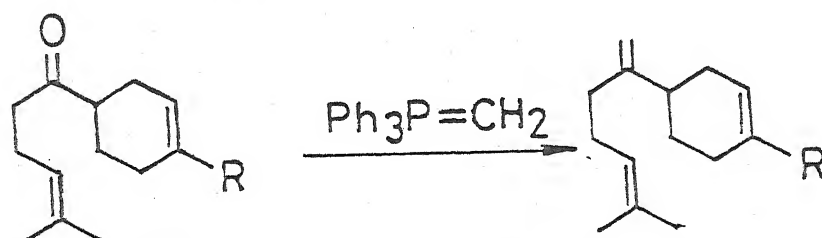
Scheme I-62



Scheme I-63



Scheme I-64



R = CH₃ (±) Bisabolene

R = -CH₂OH (±) Lanceol

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The presence of excess of either reactant increases the proportion of the Cis -isomer. And so does the addition of nucleophiles and salts such as lithium iodide.¹⁴⁹

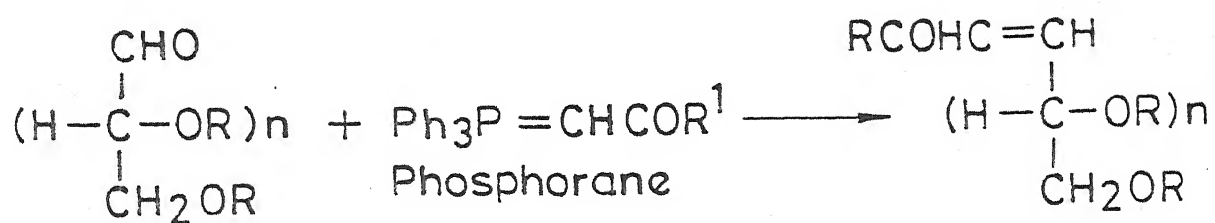
Thus by proper control of reaction conditions, Wittig reaction becomes a strong tool for the stereoselective synthesis of olefins.¹⁴⁹

Other factors such as solvent,¹⁵² Inorganic halides,¹⁵³ acid catalysis,¹⁵⁴ reactant ratio,¹⁵² reaction time¹⁵² and temperature¹⁵⁵ are also important in determining the course of the Wittig reaction.

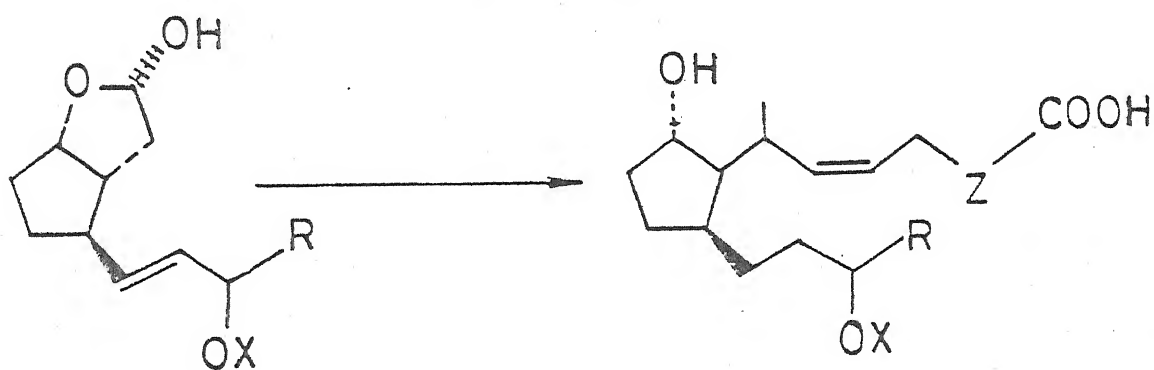
APPLICATIONS OF WITTIG REACTIONS :

The Wittig reaction has been used in the synthesis of a broad spectrum of natural products such as terpenoids - phytone,¹⁵⁶ β - bisabolene¹⁵⁷ and lanceol¹⁵⁸ (Scheme I.64); plant pigments such as β - carotene¹⁵⁹ and lycopene,¹⁶⁰ Vitamins A¹⁶¹ and D.¹⁶² Phosphonium ylides have also been used for extending the sugar chain in carbohydrate chemistry¹⁶³⁻¹⁷⁵ (Scheme I.65). This reaction has also found extensive application in the synthesis of 11 - deoxyprostaglandins¹⁶⁶ (Scheme I.66), macrocycles¹⁶⁷ (Scheme I.67) and heterocycles¹⁶⁸ (Scheme I.68).

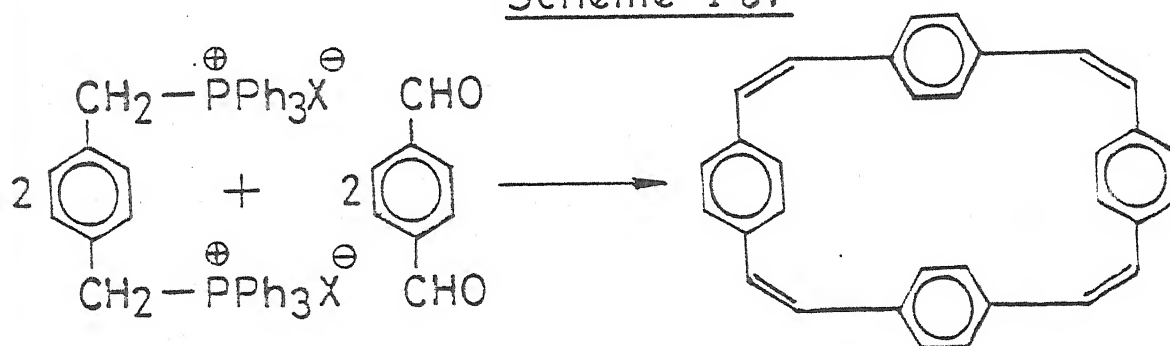
Scheme I-65



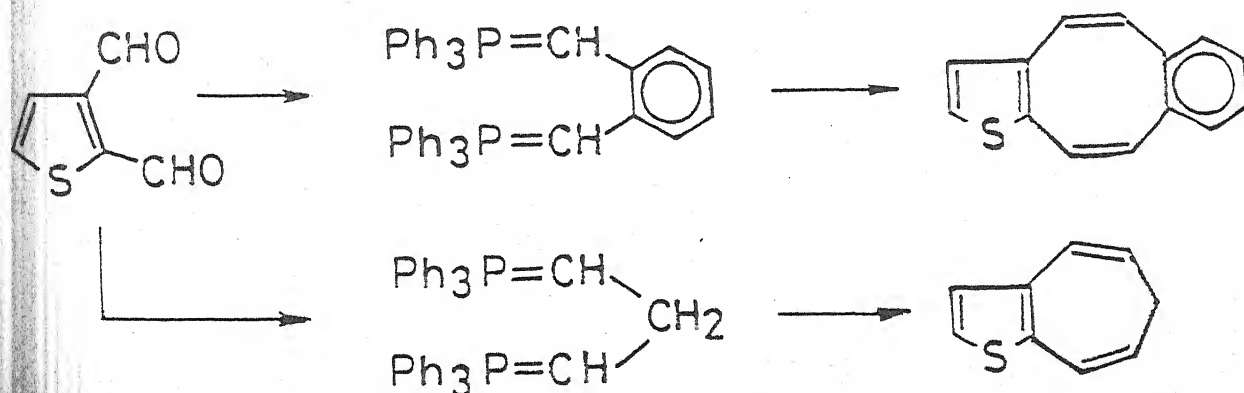
Scheme I-66



Scheme I-67



Scheme I-68



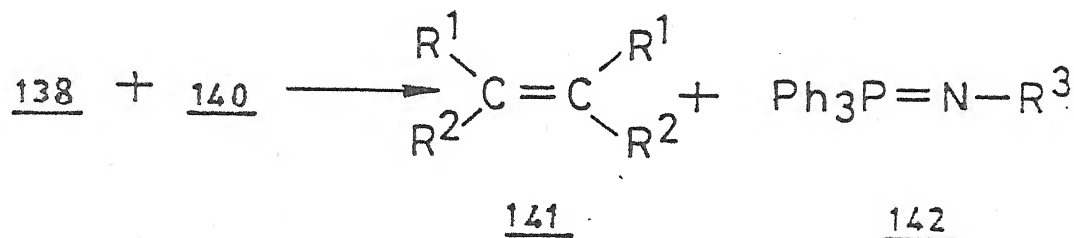
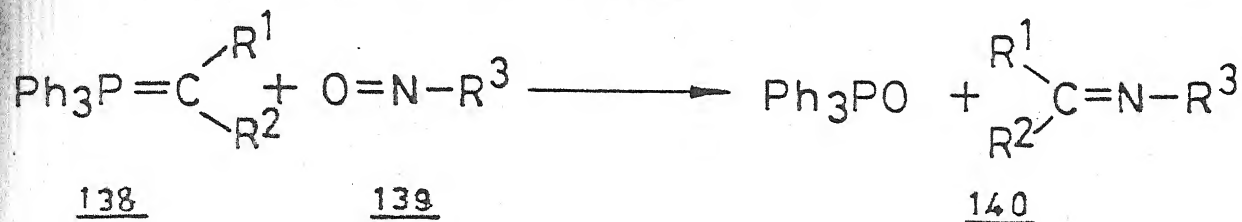
ii. With $N = O$ group : Similar to the $C = O$ group, $N = O$ containing compounds also undergo Wittig reaction. Thus, the reaction of nitroso compounds with phosphonium ylides (138) leads to the synthesis of $C - N$ double bond systems (139) which, on further reaction with a mole of the parent ylide, gives olefin (141) and iminophosphoranes¹⁶⁹ (142) (Scheme I.68).

iii. Reaction with $C = N$ group : Ylides (143) which lack $\beta - CH_2$ group, react with Schiff's bases (144) to give olefins (145) and iminophosphoranes (146) (Scheme I.70). But the ylides (147) having $\beta - CH_2$ group follow a different course on their reaction with benzaniline (148) giving allenes (150) via the intermediacy of betaine (149) (Scheme I.70b).

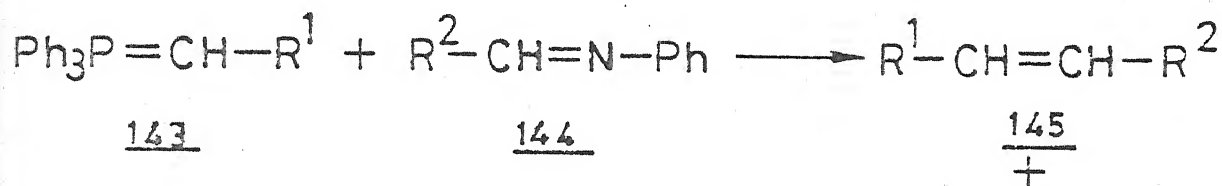
iv. Reaction with nitriles : Benzedentriphenylphosphorane (151) reacts with benzonitriles (152) to yield iminophosphorane (154) via the formation of a cyclic product (153) as the intermediate.¹⁷⁰ The hydrolysis of (153) leads to ketones¹⁷¹ (Scheme I.71).

v. Reaction with carbon-carbon triple bond : Phosphonium ylides (156) with acetylenedi-

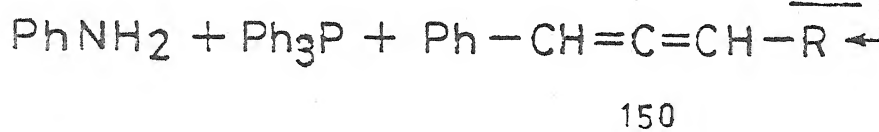
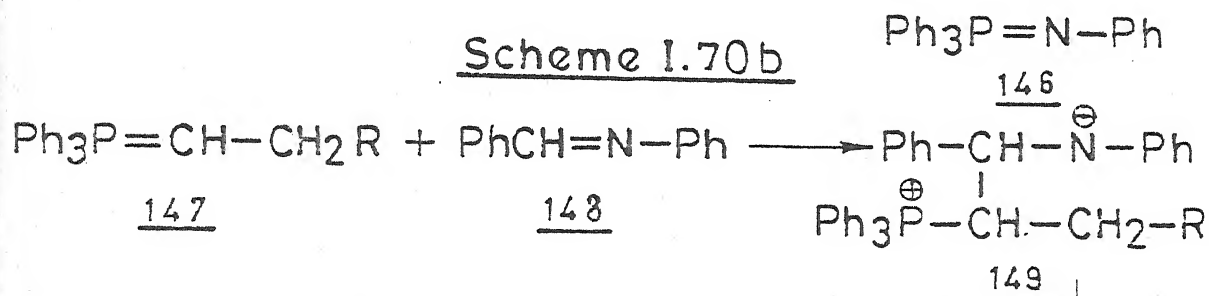
Scheme I-69



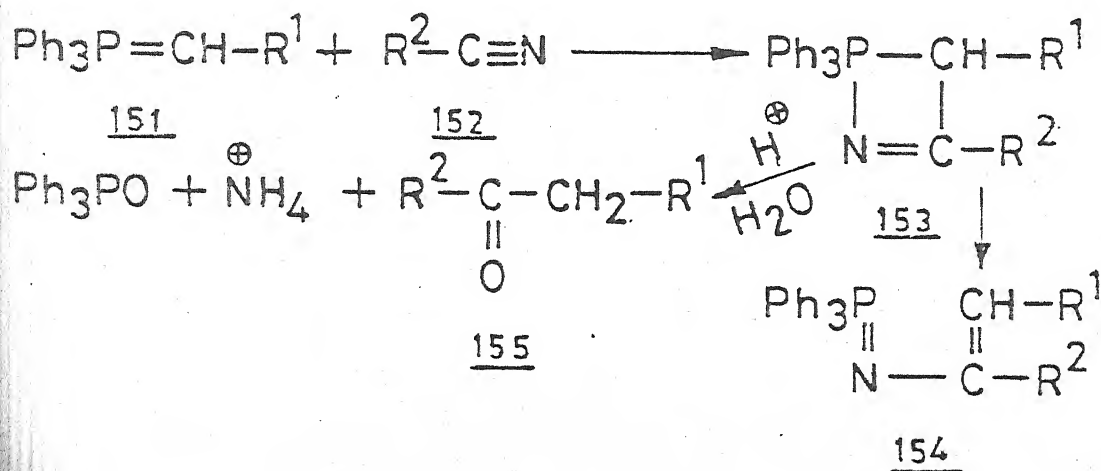
Scheme I-70



Scheme I-70b



Scheme I-71



//29//

carboxylic acid esters (157) to form phosphacyclobutene (159) either through betaine formation (158) or direct cycloaddition. The product (159) undergoes ring opening to give the stable phosphorane¹⁷² (160) (Scheme 1.72).

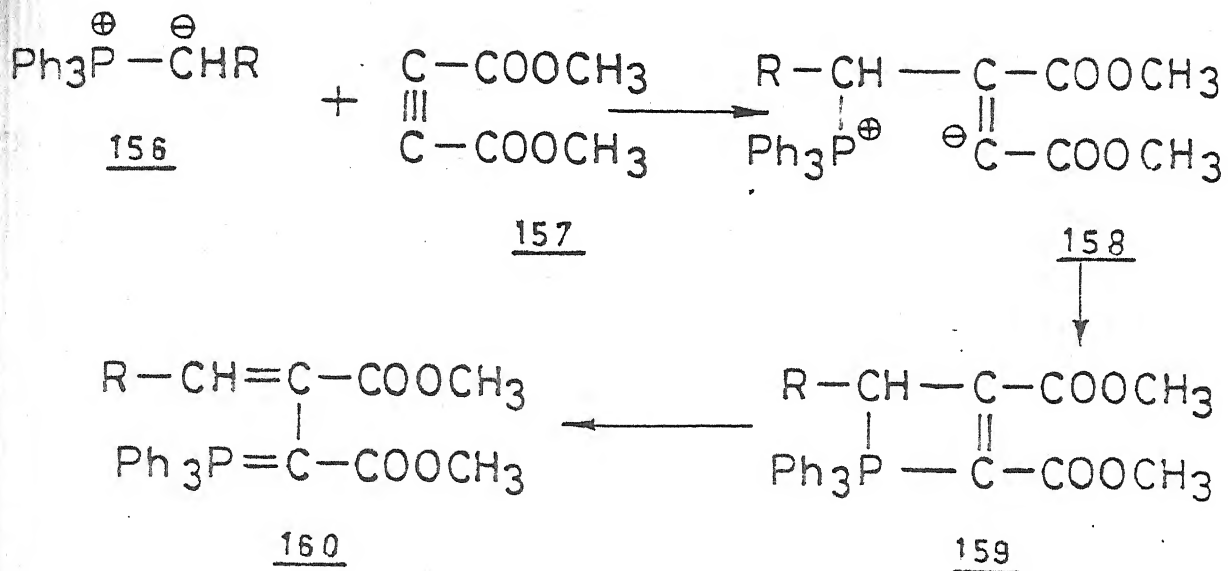
(D) Reactions with 1,3-dipolar compounds :

i. Reaction with azides : The reaction of phenylazide¹⁶¹ with benzyledenetriphenylphosphorane (162) forms benzalamine (163) and N - phenyl - triphenylphosphininine¹⁷³ (164) with the evolution of nitrogen (Scheme 1.73).

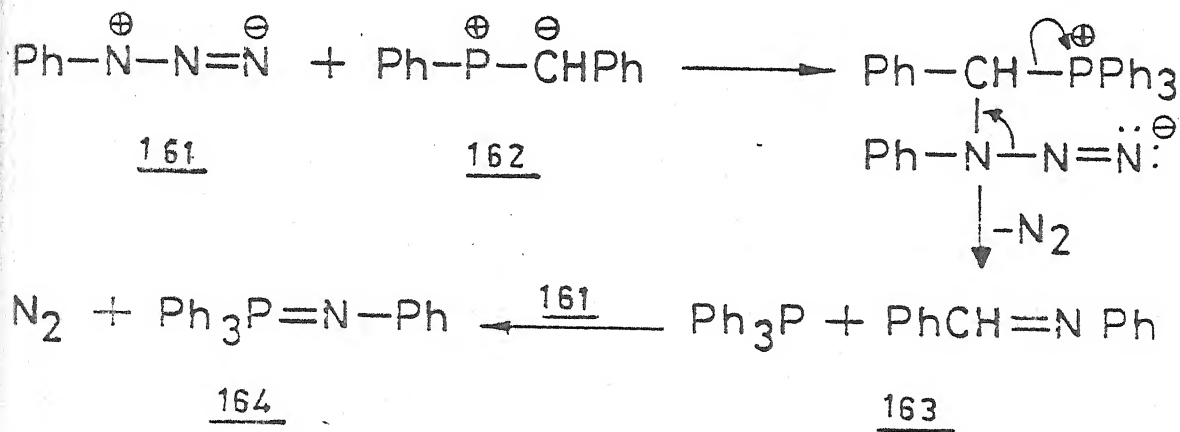
ii. Reaction with nitrones : Phosphonium ylides (166) add to nitrones (165) to form a new heterocyclic system i.e. 1,2,5 - P(V)- oxazaphospholidines¹⁷⁴ (167) (Scheme 1.74). It appears that the addition proceeds by one step multiple centre process.¹⁷⁵

iii. Reaction with nitrile oxide : Phosphonium ylides (168) and nitrile oxide (169) interact together to yield 4,5 -dihydro- 1,2,5 - P(V) - oxazaphospholenes (170) which are liable to decompose thermally¹⁸⁹⁻¹⁹⁰ depending upon the nature of substituents R, R¹ and R² (Scheme 1.75). Groups R¹ and R² with - I and - M effects cause the formation of keteneimines (171) while electron donating R¹ and R² groups cause the formation of

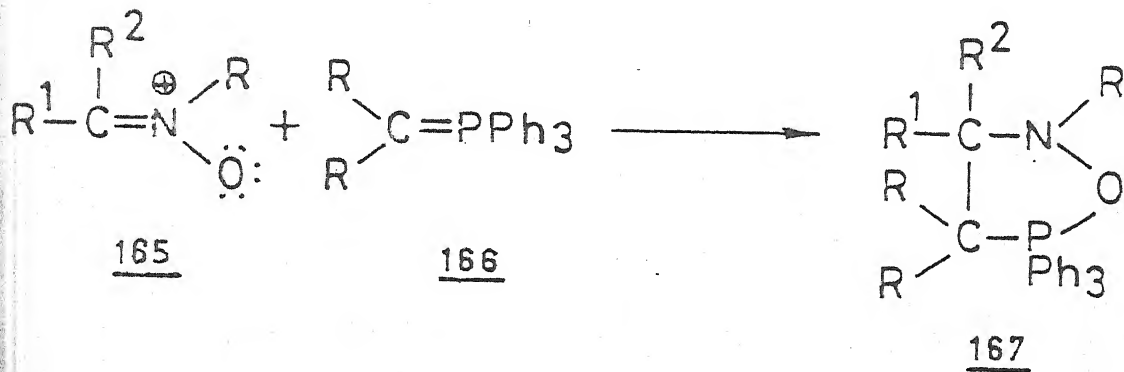
Scheme 1-72



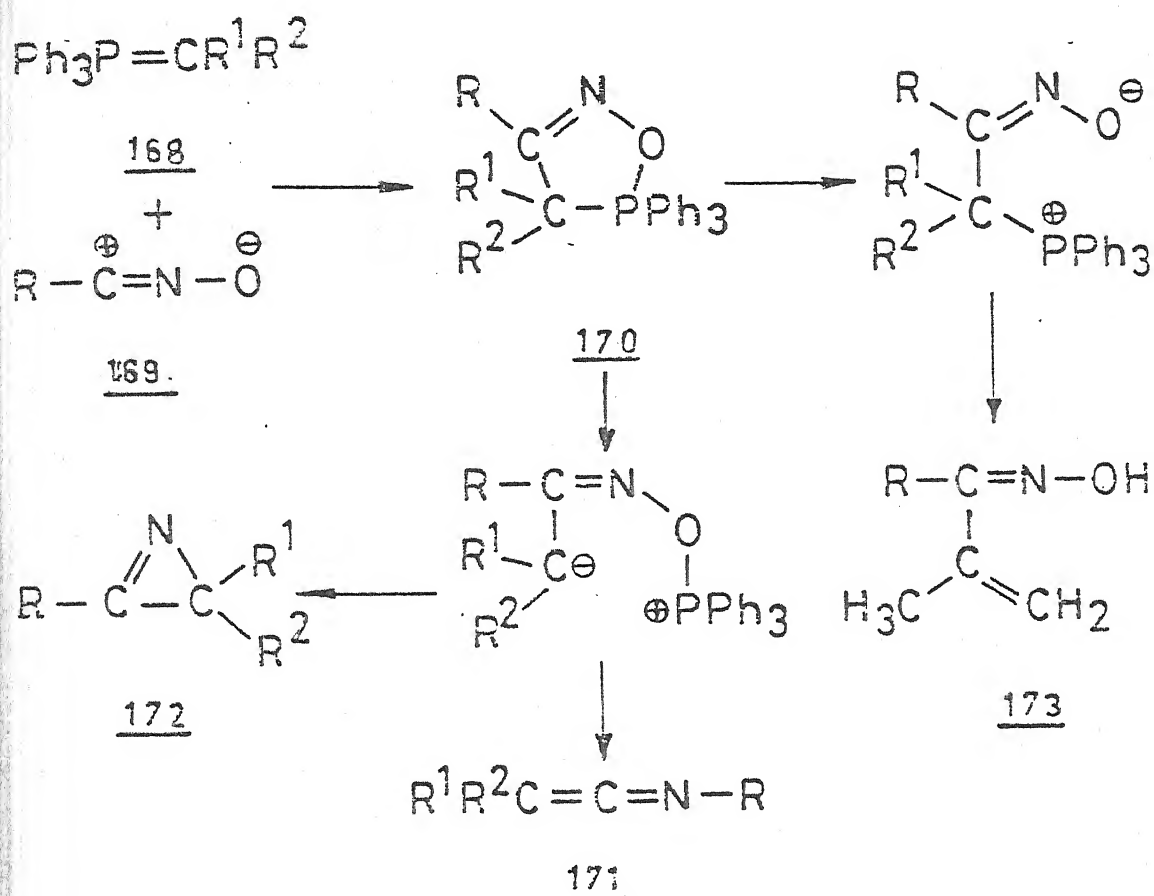
Scheme 1.73



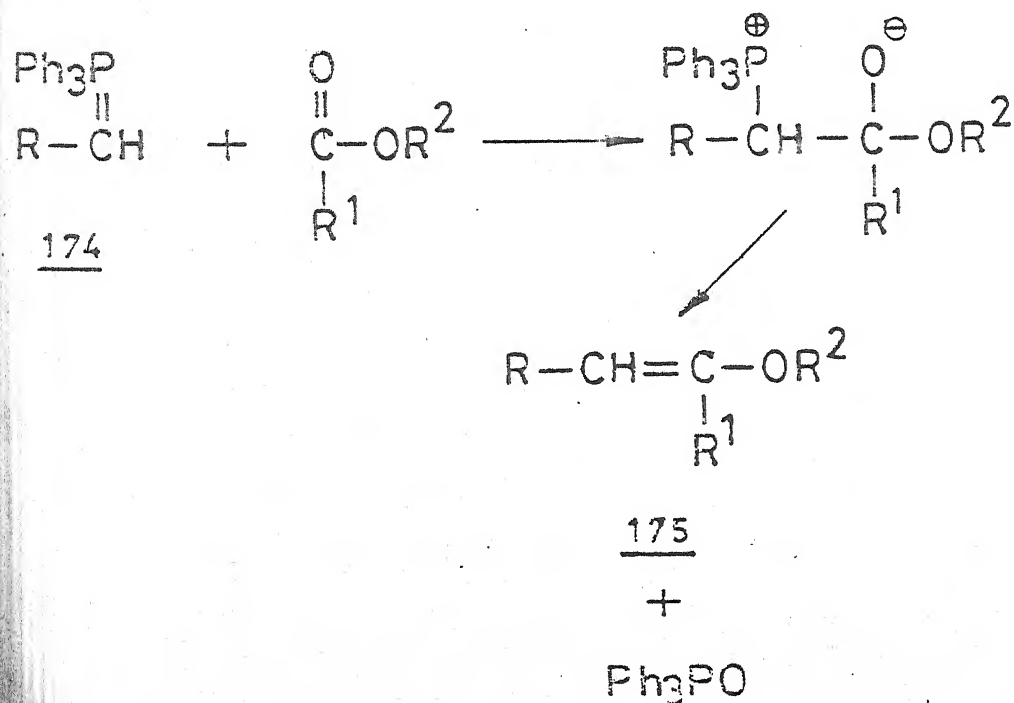
Scheme 1-74



Scheme I-75



Scheme I-76



//30//

azirines (172). If R exhibits -I effect and simultaneously R^1 and R^2 show +I effect, triphenylphosphine and α, β -unsaturated oximes (173) are formed.¹⁷⁶

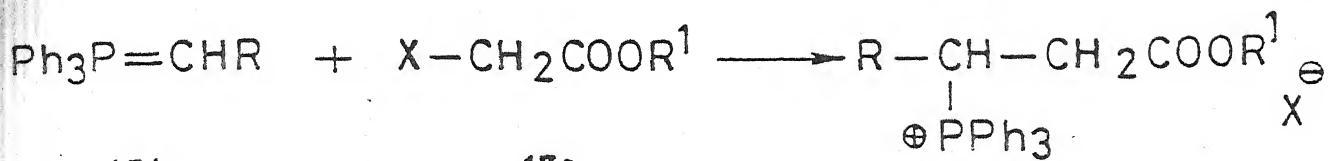
(E) Reaction with esters :

Recent investigations¹⁷⁷ have shown that reaction of phosphonium ylides (174) with ethyl formate gives substituted vinyl ethers (175) through Wittig reaction (Scheme I.76) instead of aldehydes as reported earlier.¹⁷⁸ But on the contrary, α -iodo- and α -bromoacetic acid esters (176) form phosphonium salts (177) using ylides (174) from which by transylidation reaction, a new ylide (178) is formed¹⁷⁹ (Scheme I.77). But the mono-, di- and trifluoroacetic acid esters (179) and phosphonium ylides (180) undergo a Wittig reaction to form enolethers (181) of fluoroketones¹⁷⁹ (Scheme I.78).

(F) Reaction with lactones :

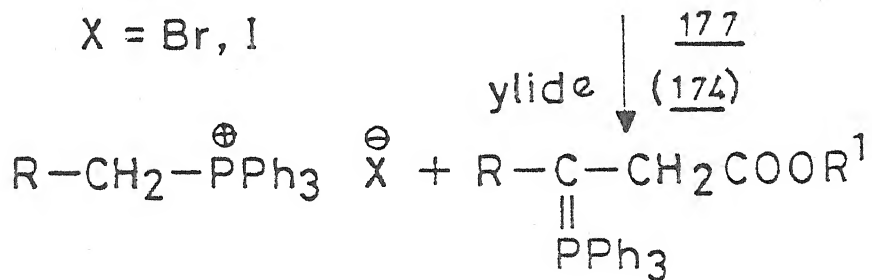
β -propiolactone (182) and γ -butyrolactone (183) react with alkylidenetriphenylphosphoranes (184) to form phosphinocarboxylate betaine (185). The thermolysis of the product (185) gives triphenylphosphine and lactones (186) with alkylidene group of the parent phosphorane (184) introduced in the ring¹⁸⁰ (Scheme I.79). But enol lactone (187) with stabilized ylides (188) give normal Wittig

Scheme 1-77



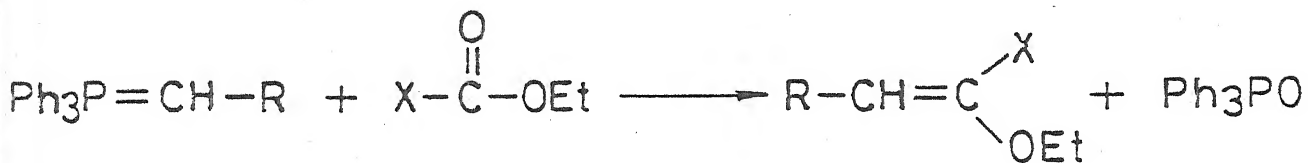
174

176

$$X = \text{Br, I}$$


178

Scheme 1-78



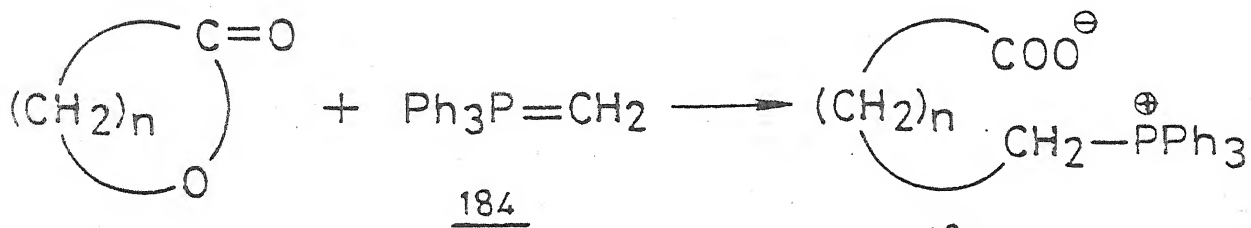
180

179

181

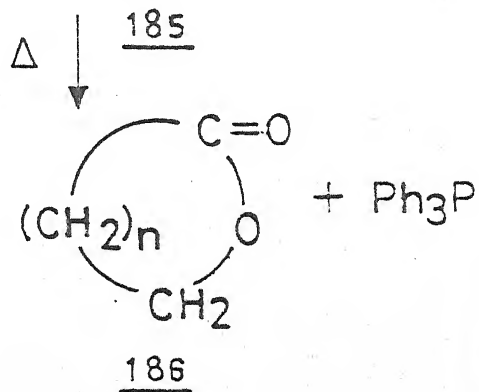
$$X = \text{CH}_2\text{F}, \text{CHF}_2, \text{CF}_3$$

Scheme 1-79



182, n = 2

183, n = 3



products¹⁸¹ (189-190) (Scheme 1.80).

(G) Reaction with cyanohydrine :

The phosphonium ylide (191) reacts with substituted benzaldehydecyanohydrine (192) in presence of $\text{NaOC}(\text{CH}_3)_3$ to form stilbenes (193 a-b) having E,Z configuration. The course of reaction is similar to Wittig reaction¹⁸² (Scheme 1.81).

(H) Reaction with chalcones :

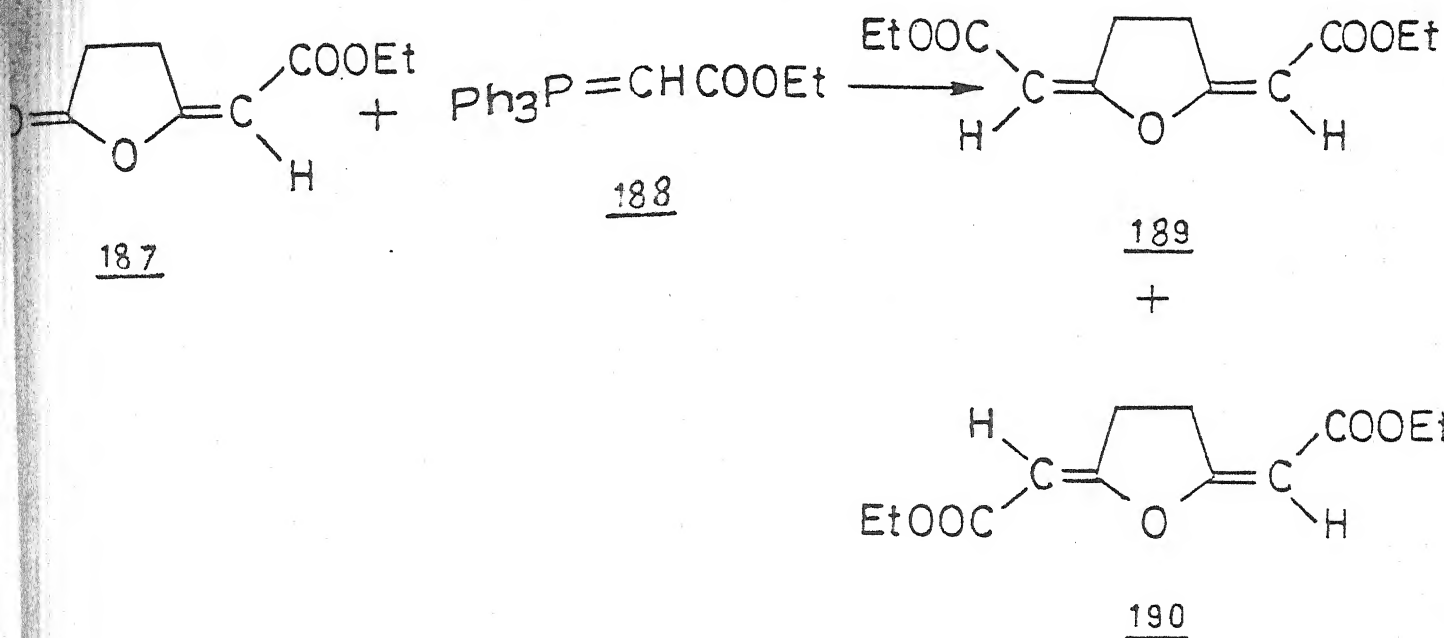
The course of reaction of phosphonium ylides with carbonyl systems is quite different to that of analogous pyridinium salts. But the reaction of phosphonium ylides (194) with α, β -unsaturated ketones (195), so called chalcones, in presence of ammonium acetate leads to azo ring closure to form 2,4,6-triaryl - pyridines¹⁸³ (196) analogous to pyridinium,¹⁸⁴⁻⁵⁷ sulfonium¹⁸⁸ and arsonium ylides¹⁸⁹ (Scheme 1.82).

(I) Reaction with N - sulfinylamine :

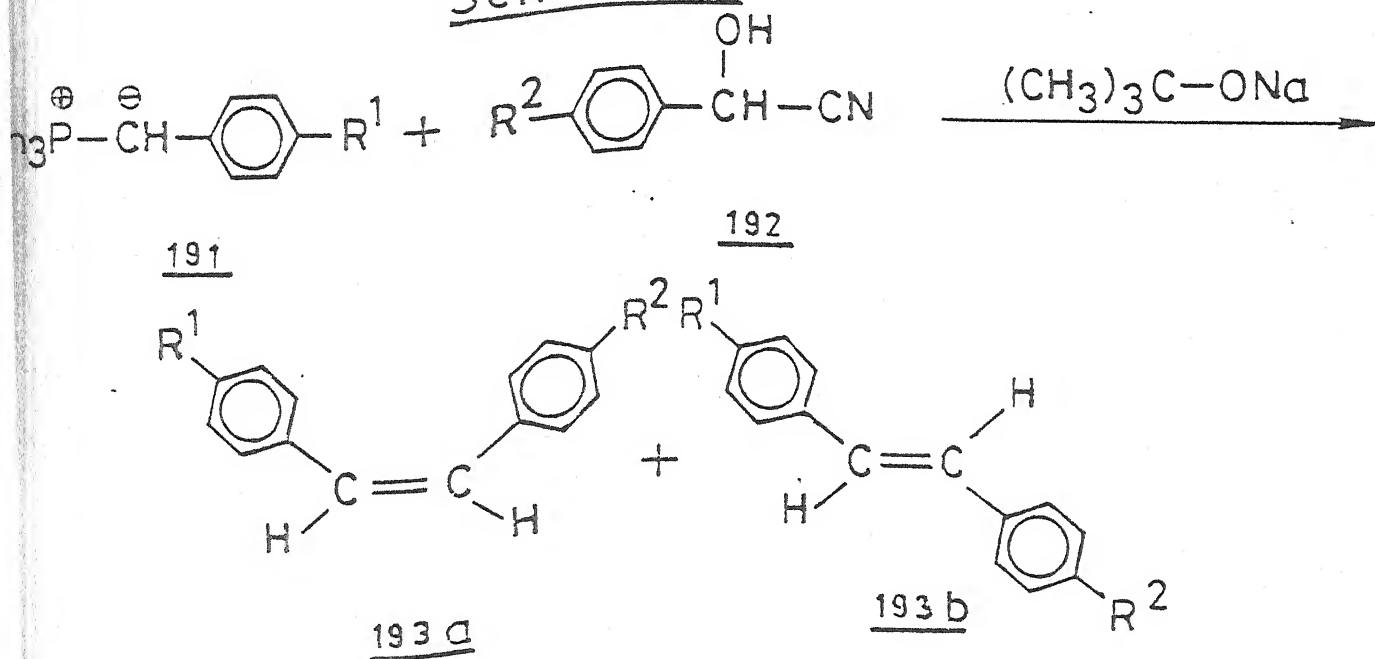
N - sulfinylamine reacts with stable phosphonium ylides to afford different products depending upon the nature of the group R attached to the nitrogen atom of the sulfinylamine.¹⁹⁰

Thus, substituted fluoroenylidene

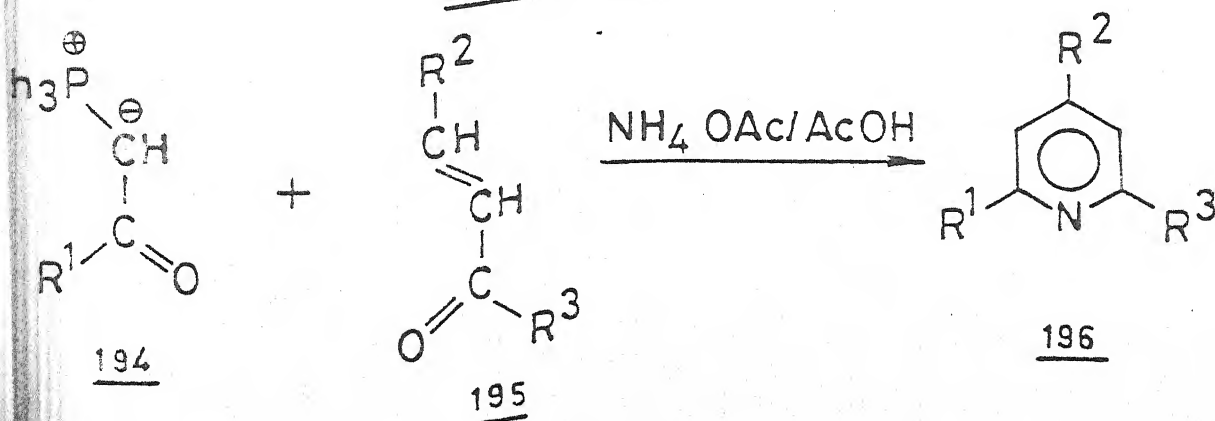
Scheme I-80



Scheme I-81



Scheme I-82



triphenylphosphoranes (198) react with N - sulfinyl - p - toluenesulfonamide (197a) on S = O bond of (197a) to give S - inide (199) and phosphine oxide analogous to Wittig reaction. But the same ylides (198) attack on the N = S bond of N - sulfinyl - p - nitroaniline (197b) to yield sulfines (200) and iminophosphoranes (201) (Scheme I.83).

1.4. π -SULFURANES (S - YLIDES) :

1.4.1. GENERAL REMARKS :

The earliest attempt to prepare sulfur ylides can be traced back to 1930 when Ingold and co-workers¹⁹¹ isolated a stabilized π -sulfurane viz. 9 - fluorenyldimethylsulfurane (203) by the reaction of dimethylsulfonium bromide (202) with aqueous sodium carbonate (Scheme I.84). This was followed by a lull as nothing was added to the literature concerning reactivity and synthetic potentialities of this class of compounds for a considerable period of time.

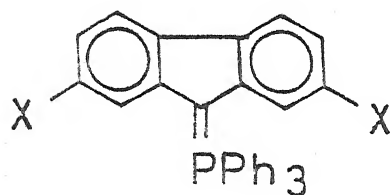
Having come to the conclusion that any molecular system with an ability to provide adequate stabilization to a carbanion may form an ylide¹⁹² and encouraged by Wittig investigations on phosphonium ylides, Johnson et al¹⁹³ reported the successful isolation of fluorenylidenedimethyl sulfurane (203). This ylide was sufficiently stable due to

Scheme 1-83

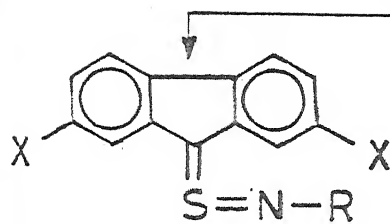


197 a-b

+

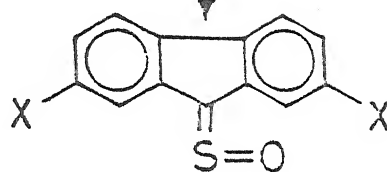
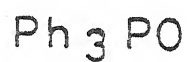


198



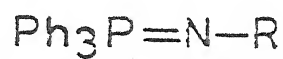
199

+

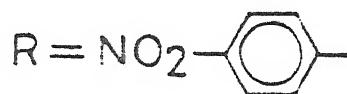
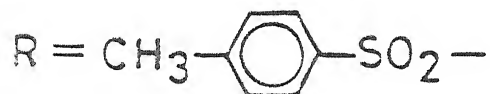


200

+



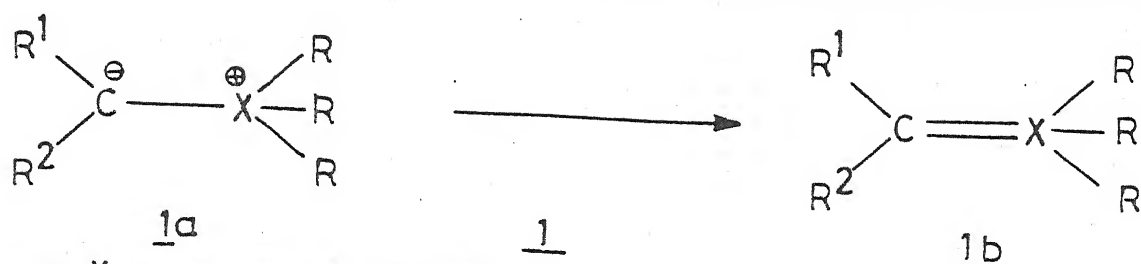
201



delocalisation of the lone pair of electrons present in ylidic carbanion as shown by the resonating forms (203a, b,c). This prevented it from entering into reaction with electrophilic reagents.¹⁹⁴ Even their attempt to react the ylide (203) with benzaldehyde to form 9-benzalfluorence (204) failed when benzal-fluorine oxide (205) and phenyl - 9 - (1-methylthiomethyl) fluorenyl carbinols (206) were formed instead (Scheme I.85).

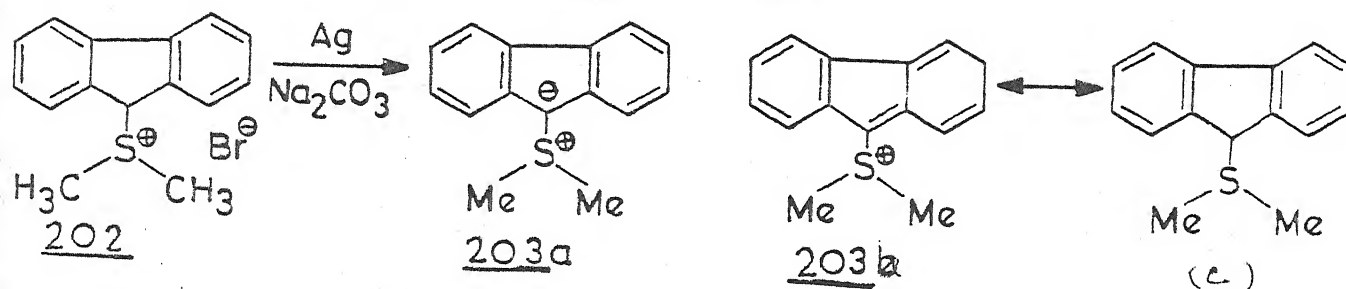
Later, Corey et al¹⁹⁵ prepared and studied the reactions of a less stable and more reactive ylide viz. methylene - dimethyloxosulfonium ylide (207). Taking a cue from the ability of phosphonium ylides acting as good carbonyl olefinating reagents,¹⁹⁶ Corey and co-workers¹⁹⁷ reacted the oxosulfonium ylide (207) with aldehydes and ketones (208). But instead of getting olefins, epoxides (209) were the exclusive products (Scheme I.86). This reaction earned for oxosulfonium ylides a status of useful epoxidation reagents. Consequently, a flurry of activity started to explore the synthetic potentialities of these ylides.

Very soon Franzel and Driessen¹⁹⁸ synthesised a new class of π -sulfuranes also called the sulfonium ylides (212). These ylides could be prepared by the reaction of methylphenyl sulfide (210) with methyl iodide (211) followed

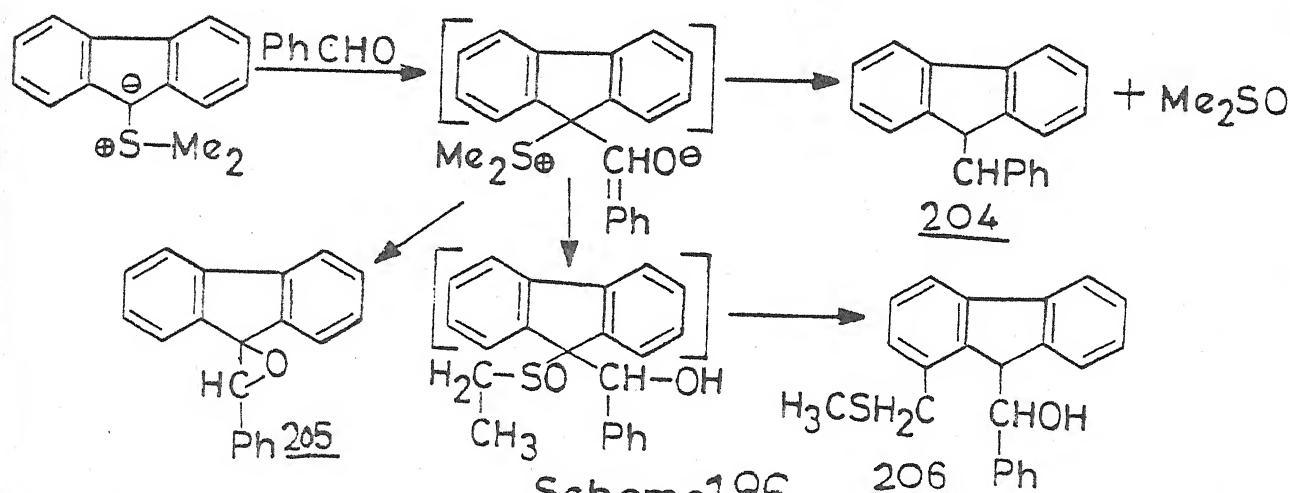


(where X may be N, P, As, S, etc.)

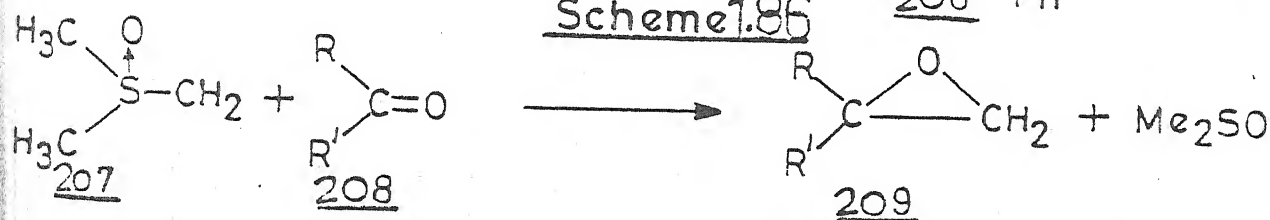
Scheme 1.84



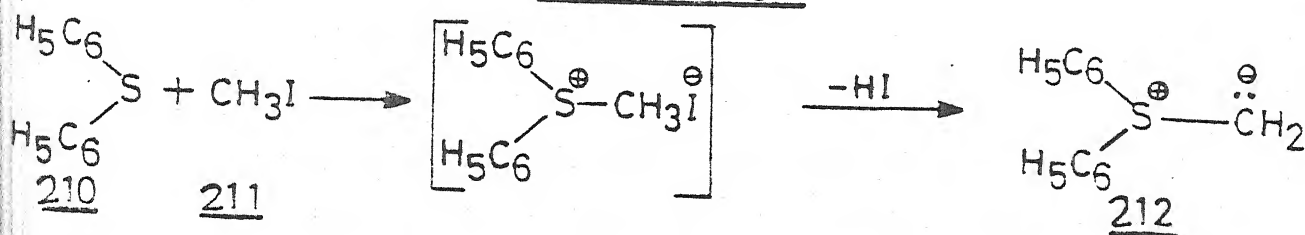
Scheme 1.85



Scheme 1.86



Scheme 1.87



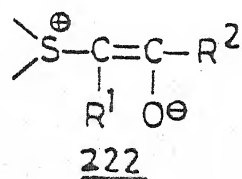
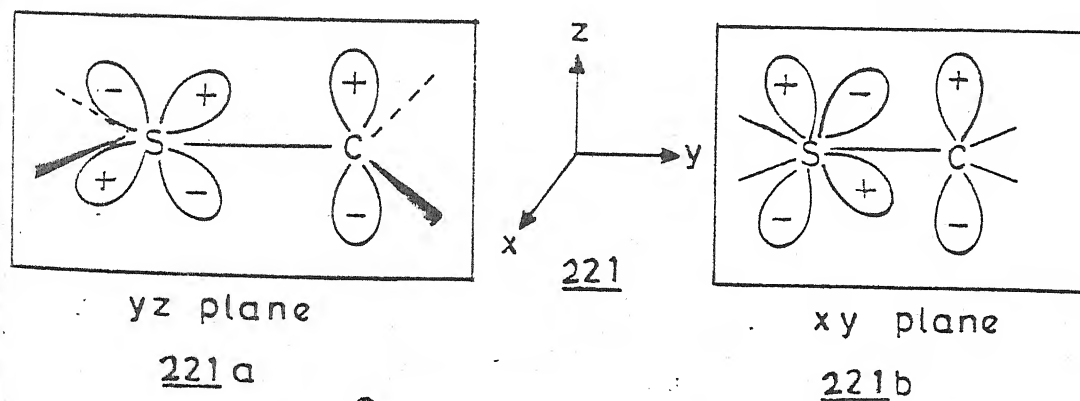
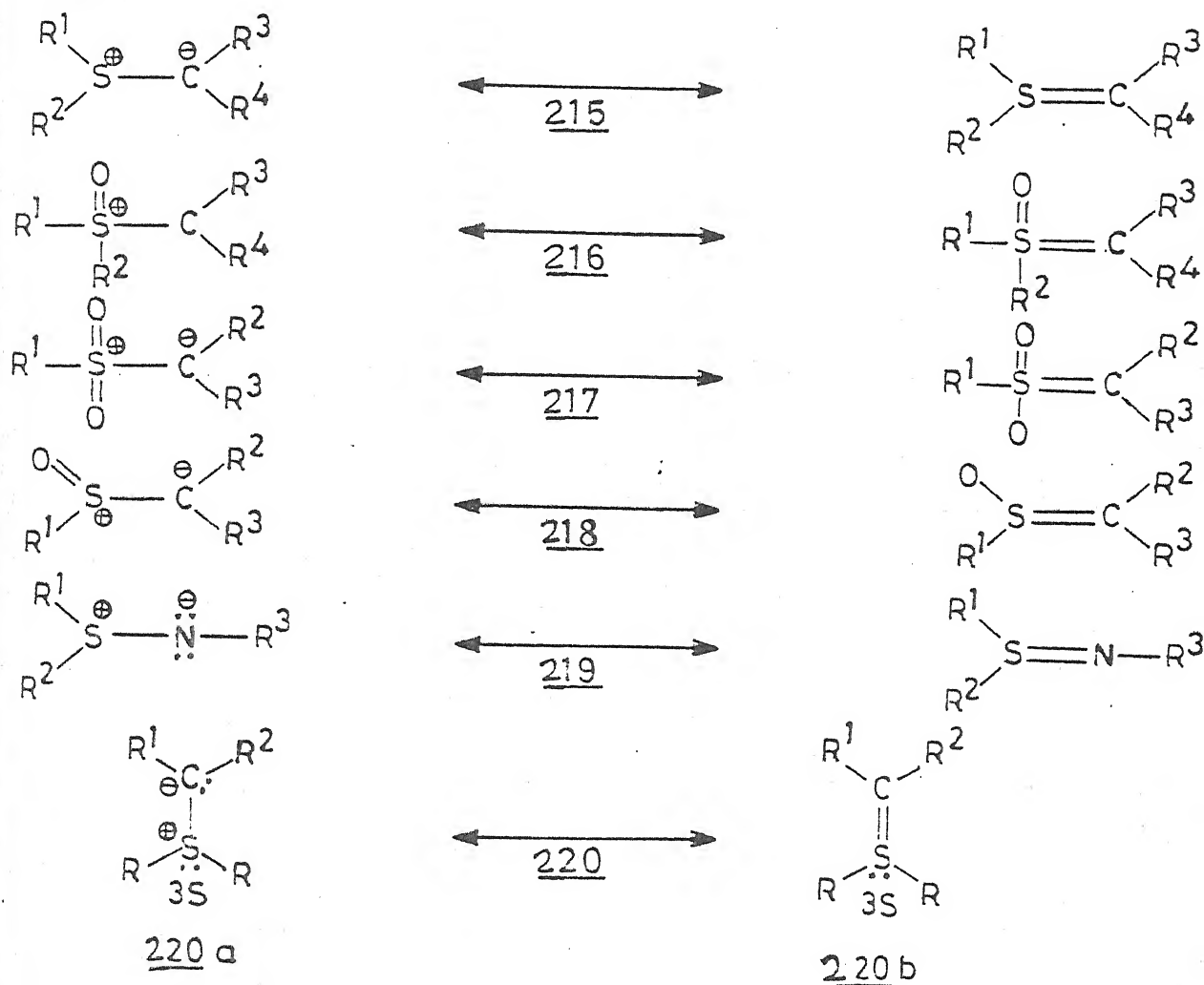
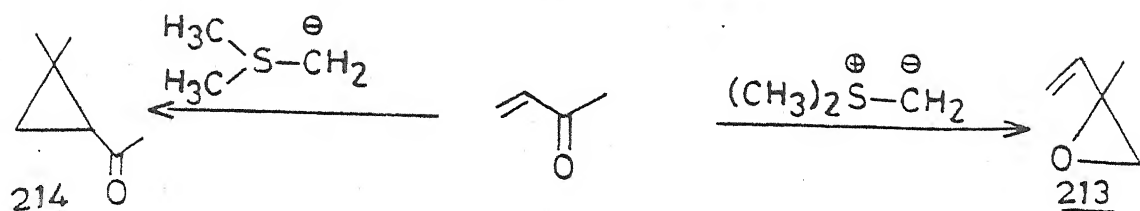
by dehydrohalogenation (Scheme I.87). The ylide (212) was less stable than the oxosulfonium ylide (207).

In their subsequent investigations Corey and Chaykovsky¹⁹⁹ could show that sulfonium ylides do not only undergo methyl transfer reaction on carbonyl group to form epoxides but also add on to the C = C bond having unsaturated group in conjugation to form cyclopropanes. Thus, while methylenedimethylsulfurane has earned the distinction of being a good epoxidation reagent to form Oxiranes (213), oxosulfoniummethylide adds to the activated C = C group to form cyclopropanes (214) (Scheme I.88).²⁰⁰⁻²⁰² It has now been established beyond any doubt that sulfuranes are the best methylene transfer reagents. In the recent years the investigations in the field of exploring the synthetic potentialities have expanded tremendously as evidenced by several review articles.²⁰³⁻²⁰⁹

Among the large variety of classes of sulfuranes, the more important ones are sulfonium ylides (215), oxosulfonium ylides (216), sulfonyl ylides (217), sulfinyl ylides (218) and iminosulfuranes (219).

Electrostatic stabilization and delocalization of charge on the carbon atom with d orbitals of the S atom^{210,211} are the two factors which control the stability of π -sulfuranes. The extent of electrostatic stabilization is

Scheme 1.88



solely controlled by the amount of charge present on the onium group as well as the ylidic carbon. This explains why the oxosulfonium ylides are more stable than their sulfonium counterparts. The former has enhanced positive charge on the S atom due to the presence of more electronegative oxygen atom. The second factor viz. delocalization involves use of 3d orbitals which is maximum if the α -sulfur atom carries a full unit of positive charge. Thus, the overlap of the doubly occupied 2p orbital of the ylidic carbon with the vacant 3d orbital of S atom occurs to form a π bond while the lone pair in the sulfur atom remains in 3p orbital. It is possible to represent it as the resonance hybrid of two limiting structures (220a and 220b).

It is now easy to appreciate why a large number of π -sulfuranes have been isolated and characterised as stable species.

It may be noticed that the maximum overlap of 2p orbital of carbon (221a) with 3d orbital of sulfur is possible only when the molecule tends to be coplanar (221b). The resultant $p\pi - d\pi$ orbital overlap can be represented by the structure (222).

Recent ESCA data has shown that the stability of these ylides is also affected by the presence of some

electronegative groups on the ylide carbon.

The properties of carbanion as well as the possible involvement of the heteroatom determines the reactivity of the π -sulfuranes.^{199,212-221} Generally the alkylidene sulfuranes of low stability exhibit high reactivity whereas highly stable alkylidene sulfuranes are comparatively much less reactive.

The reactivity of the alkylidene sulfuranes depends upon the distribution of the negative charge over the molecule which, in turn, depends on the nature of substituents R^1 and R^2 in alkylidene position as well as on the group R on the sulfur atom. One may, therefore, conclude that as the nucleophilic character of the sulfuranes decreases and its stability increases if the lone pair of electrons on the α - carbon atom of the ylide (220a) is delocalised into R^1 and R^2 . The electron withdrawing groups R^1 and R^2 tend to stabilize the negative charge and hence reduce the reactivity of the ylide. But when there are no such interactions, an extremely unstable and reactive ylide is the result.

1.4.2 GENERATION OF SULFONIUM YLIDES :

(A) Ylides from sulfonium salts :

Like other ylides, the most common and widespread

method^{200,222-230} for the generation of sulfonium ylides involves the reaction of the sulfonium salt with a base which is sufficiently strong to pull out a proton from the α - carbon atom.

In theory, all sulfonium salts (223) with at least one α - hydrogen can be converted into an ylide (224) (Scheme I.89). In practice, however, the salt method is applicable only in three structural situations.

- (i) All the three groups attached to the sulfur atom are identical.
- (ii) One or two of the substituents have no α -hydrogen atoms. But the groups (if more than one i.e. two) having α - hydrogen atoms must be identical.¹⁹⁸
- (iii) There is appreciable difference in acidity of the various available α - hydrogen atoms and a base of appropriate strength is available.^{191,231}

In the above context, the deprotonation of the more acidic α - hydrogen atom is almost invariably preferred. If the sulfonium salt (225) has three types of α - hydrogen atoms of comparable acidity, a mixture of sulfonium ylides (226), (227) and (228) is formed (Scheme I.90).

A large number of bases have been used to generate

sulfonium ylides. The strength of the base to be used depends on the acidity of the corresponding sulfonium salt. Thus, for example, trialkylsulfonium salts require quite strong bases such as methyllithium,²³² potassium t.butoxide^{193,233} in dimethylsulfoxide etc. Generation of stabilized ylides requires only weak bases such as triethylamine, aqueous ammonia or aqueous sodium hydroxide. Bases such as dimethylsulfoxide or tetrahydrofuran can be used to generate non-stabilized sulfonium ylides. Protic solvents or water are not suitable as they react with non-stabilized sulfonium ylides.

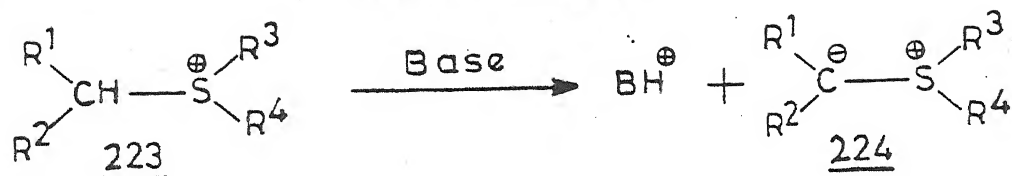
(B) Ylides from benzyne and organic sulfides :

This method is of little practical importance as the presence of phenyl ring in the resulting ylide makes them less reactive due to delocalization of positive charge over the phenyl ring.²³⁰ The reaction between dialkylsulfide (229) and benzyne (230) generates the ylide (231) in which S atom carries one phenyl ring (Scheme I.91).

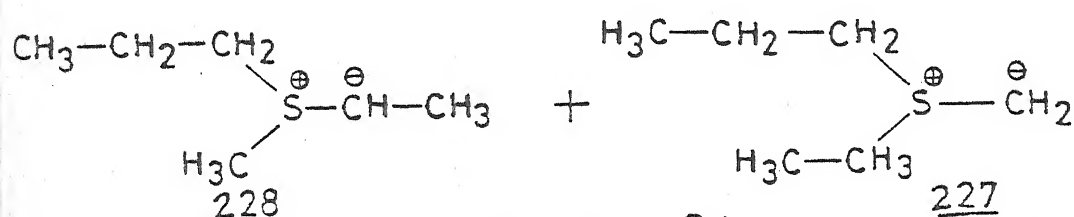
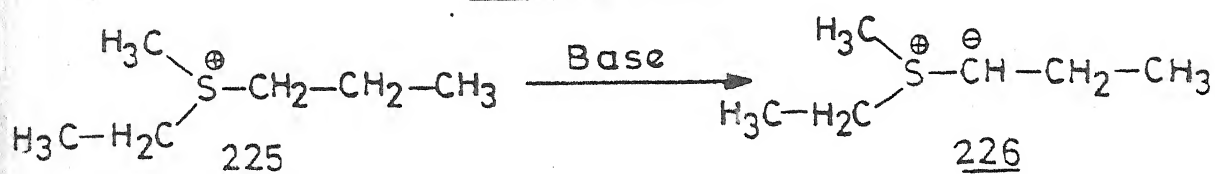
(C) Ylides from alkylation or acylation :

A number of complex ylides can be prepared by alkylation²³⁵ and acylation.²³⁶ This method involves the interaction of simple ylides with alkylating or acylating agents to form more substituted and stabilized ylides

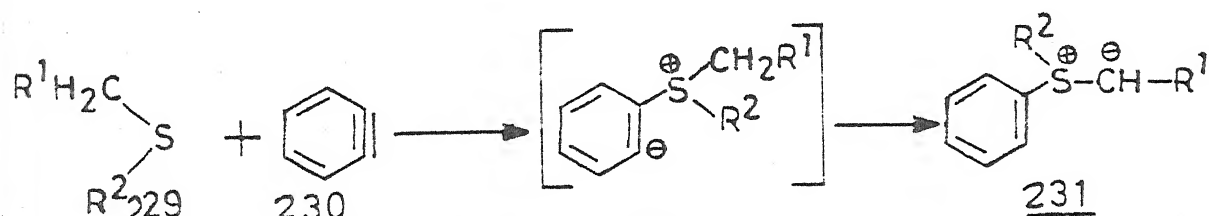
Scheme 1.89



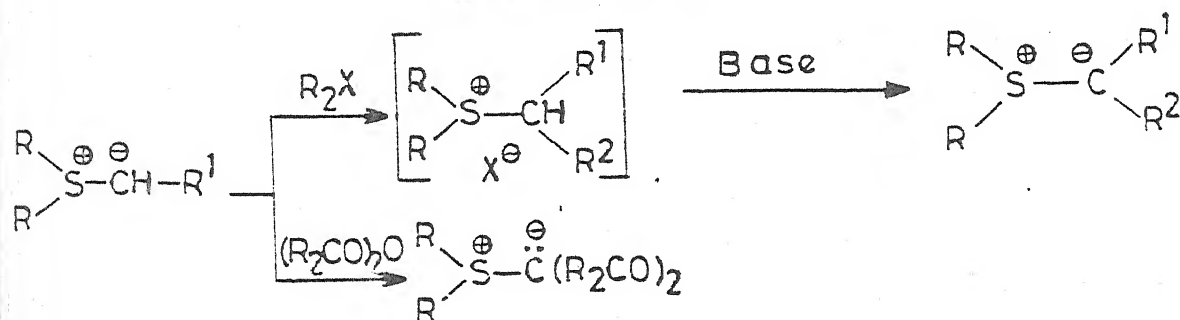
Scheme 1.90



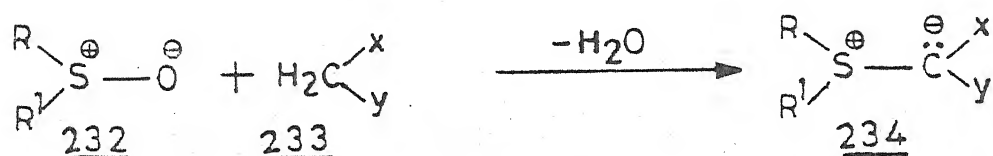
Scheme 1.91



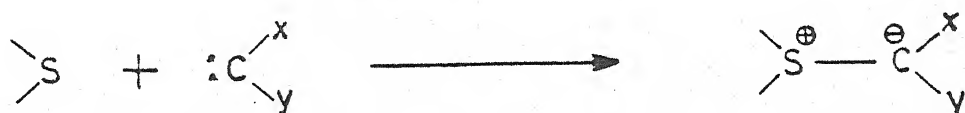
Scheme 1.92



Scheme 1.93



Scheme 1.94



(Scheme 1.92).

(D) Ylides from active methylene compounds and sulfoxide :

A direct route for the synthesis of highly stabilized ylide (234) through intermediate salt formation consists of condensation of active methylene groups (233) with sulfoxides or alkoxysulfonium salts (232)²³⁷⁻²³⁹ (Scheme 1.93).

Since the reaction is favoured in presence of dehydrating agents, generally acetic anhydride, phosphorus pentoxide or phenylisocyanate are used for the purpose.

(E) Ylides from carbenes :

The most direct route for the synthesis of S - ylides consists of addition of a carbene to a sulfide (Scheme 1.94).²⁴⁰⁻²⁴² For this purpose, diazo compounds serve as good sources of carbene intermediates, for example, in the preparation of ylide (237). Diazo compounds (236) are decomposed with Copper as catalyst and heat as the reagent or by photolysis in presence of an alkyl or benzyl sulfide (235) to yield the desired ylide (237) (Scheme 1.95). In comparative terms, thermal decomposition is better suited for ylide synthesis.

(F) Ylides via Michael addition to Vinylsulfonium salt :

The Michael addition to a vinyl - sulfonium salt

(238) also generates sulfonium ylides (239)²⁴³⁻²⁴⁴ (Scheme I.96).

(G) Ylides from electrochemical reduction of sulfonium salts :

In the only example²⁴⁵ of this type, the synthesis involves the reduction of trimethylsulfonium salt (240) in DMSO solution to give the ylide (241) (Scheme I.97).

(H) Ylides from other methods :

Phase transfer catalysis²⁴⁶ yields dimethylsulfoniummethylide in good amounts. Diphenylsulfoniumcyclopropylide²⁴⁷ is prepared in high yields by the ligand exchange reaction between triphenylsulfonium cation and cyclopropyllithium. Thirenes²⁴⁸ and Thoranes²⁴⁹ are prepared by the reaction of aldehydes and ketones with S - lithiomethyl - o - (-) methyl - dithio carbonate.

1.4.3. REACTIONS OF SULFONIUM YLIDES :

(A) With halogen acids :

Ratis²³⁴ et al first reported that phenacylidene-sulfonium ylide reacts with HBr to form dimethylphenacylsulfonium bromide. Later Johnson et al²³⁶ repeated the reaction and reported that almost all the carbonyl stabilized sulfonium ylides (242) react with HBr (243) to form a

conjugate acid (244) of the parent ylide (242) (Scheme I.98). Thus, the ylides are conjugate bases of dimethylphenacylsulfonium bromide.

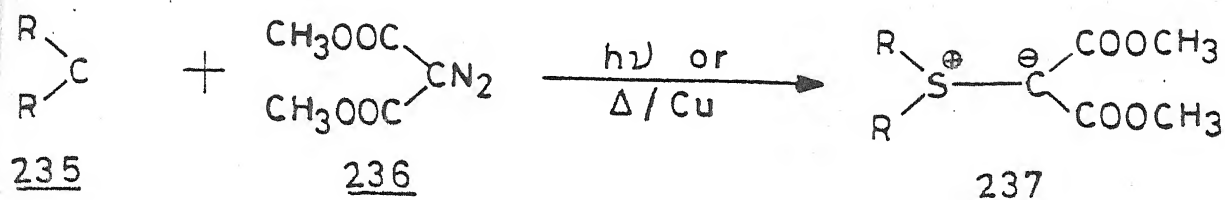
(B) Thermolysis :

Very little work has been carried out to investigate the thermolysis of sulfonium ylides. Johnson et al²³² have demonstrated that the non-stabilized sulfonium ylide, diphenylsulfonium - benzylyde (245), when subjected to thermolysis, breaks up into carbenes (246) and phenylsulfide (247) (Scheme I.99). On the other hand, stabilized ylide, phenacylidenedimethylsulfurane (248), upon thermolysis, gives different products.²⁵⁰⁻²⁵¹ The carbene generated by thermal dissociation dimerises to form dibenzoyl ethylene which is attacked by another mole of the starting ylide (248) to form 1,2,3 - tribenzoylcyclopropane (249) (Scheme I.100).

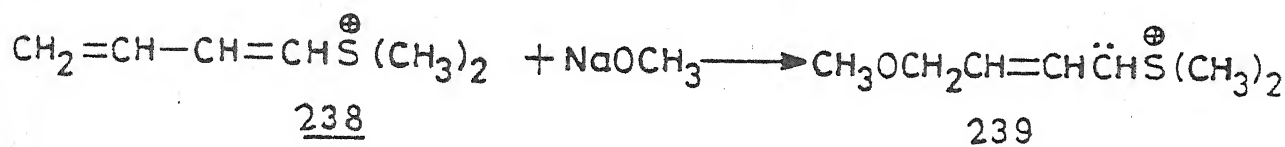
(C) Photolysis :

Not much work has been done on the photolysis of sulfonium ylides. Trost²⁵² brought about the photochemical decomposition of diphenylsulfoniumallylyde (250) to yield cyclopropane in 25% yield (Scheme I.101). Later on, Corey²⁵³ in an Arnt - Eistert type of process, irradiated β - ketooxosulfonium ylide (253) prepared by the acylation of the methyllide (252) to afford esters (254) (Scheme I.102).

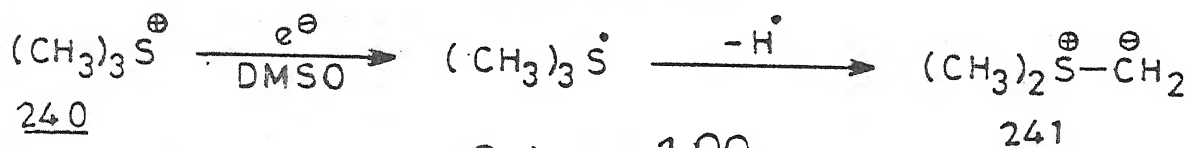
Scheme 1.95



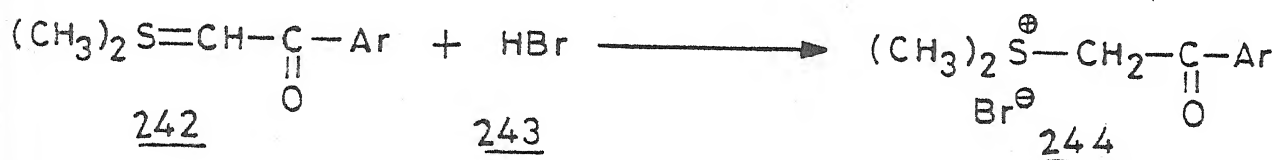
Scheme 1.96



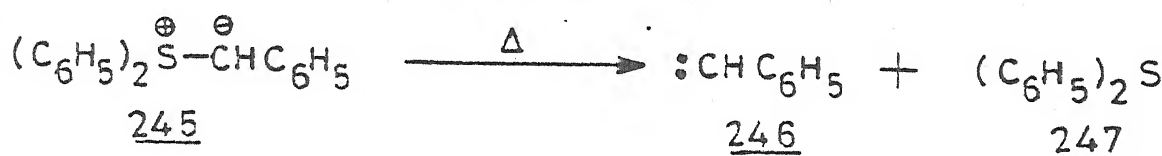
Scheme 1.97



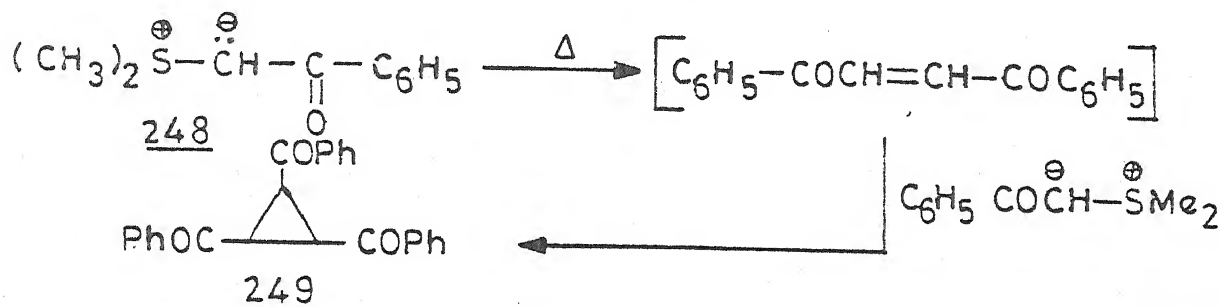
Scheme 1.98



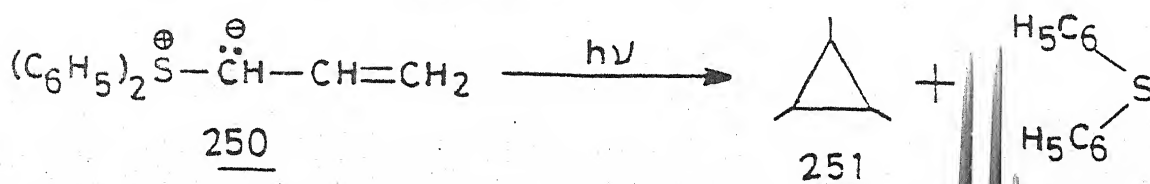
Scheme 1.99



Scheme 1.100



Scheme 1.101



(D) With α - bromoketones :

The reaction²⁵⁴ of phenacylidine - dimethylsulfurane (255) with its conjugate acid (256) or phenacyl bromide (257) yields tribenzoylcyclopropane (258).

Alkylation - elimination - addition sequence seems to determine the mechanism of the reaction (Scheme I.103).

(E) Alkylation :

Disubstituted ylides, which are otherwise difficult to synthesise, can be easily prepared by the alkylation reactions. Thus the alkylation²³⁶ of phenacylidinedimethylsulfurane (259) with benzyl bromide (260) yields α - methylthio - β - phenylpropiophenone (261) (Scheme I.104).

(F) Acylation :

It has been observed that non stabilized sulfonium ylides refuse to undergo acylation. On the other hand, stabilized sulfonium ylides have been reported to undergo acylation with a couple of acylating agents.^{236,235} However, the course of acylation reaction is determined by the nature of the acylating agent.

Thus, phenacylidinedimethylsulfurane (262) reacts with benzoic anhydride to undergo C - acylation to form a

new ylide (263). But the same ylide (262), when reacted with benzoyl chloride undergoes O - acylation to form enol benzoate (264) (Scheme I.105).

(G) With amino compounds :

A variety of substituted indoles (267) have been synthesised²⁵⁶ by the reaction of dimethylsulfonium methylides (265) with aromatic o - aminocarbonyl compounds (266) (Scheme I.106). Junjappa²⁰³ has recently reported the formation of 2 - substituted indoles (270) by the interaction of stabilized ylide, phenacylidinedimethyl - sulfurane(268) and disubstituted anilenes (269) in presence of diethylalene (Scheme I.107).

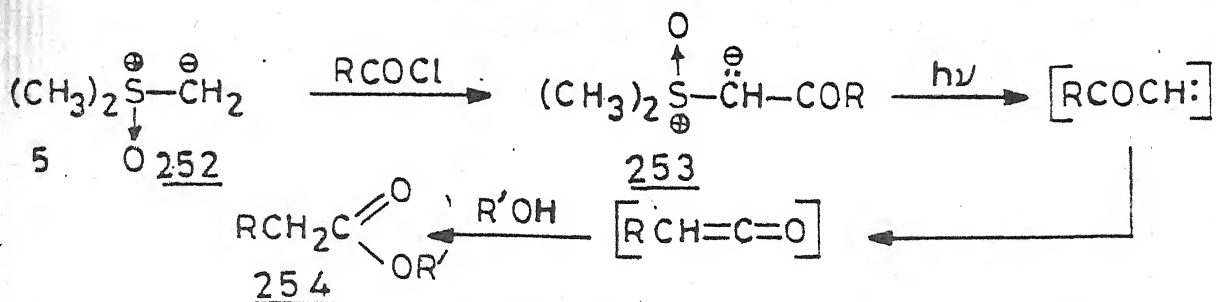
(H) With mercapto compounds :

The reaction of dimethylsulfonium-methylide (272) with O - mercaptoketones (271) to form substituted benzothio-phenes (273) has been investigated by Bravo et al²⁵⁷ (Scheme I.108).

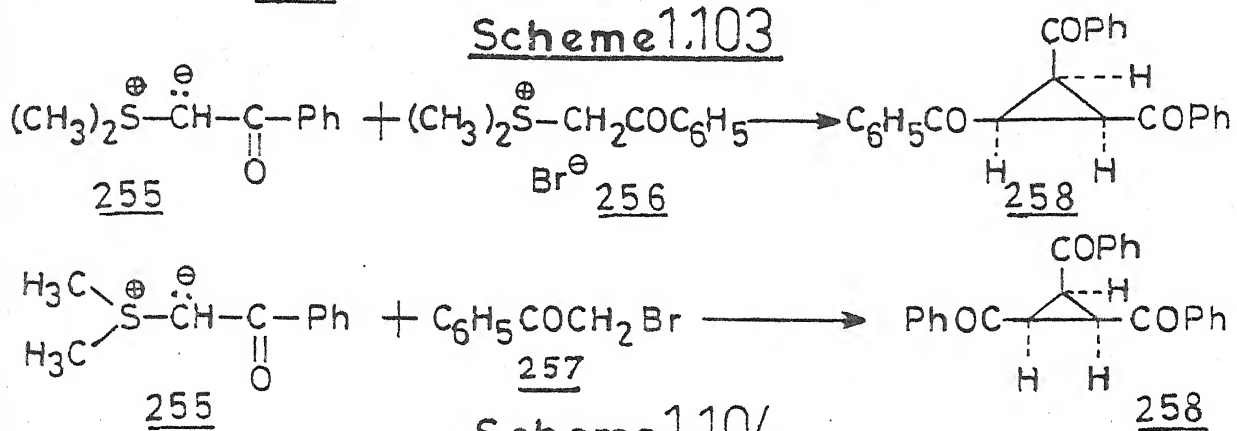
(I) With nitrileimines :

Pyrazole derivatives are obtained²⁵⁸ when carbonyl stabilized sulfonium ylides interact with nitrile-imines. Thus, the reaction of stabilized sulfurane (275) with N - (- α - Chlorobenzy - lidene) - N - phenylhydrazine (275) yields

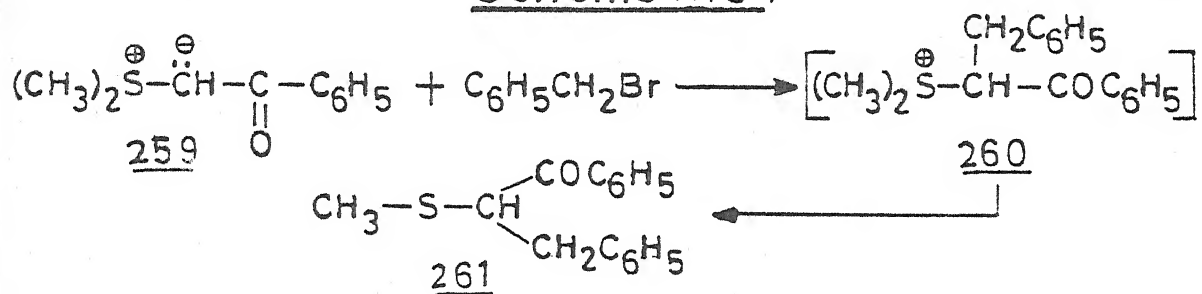
Scheme 1.102



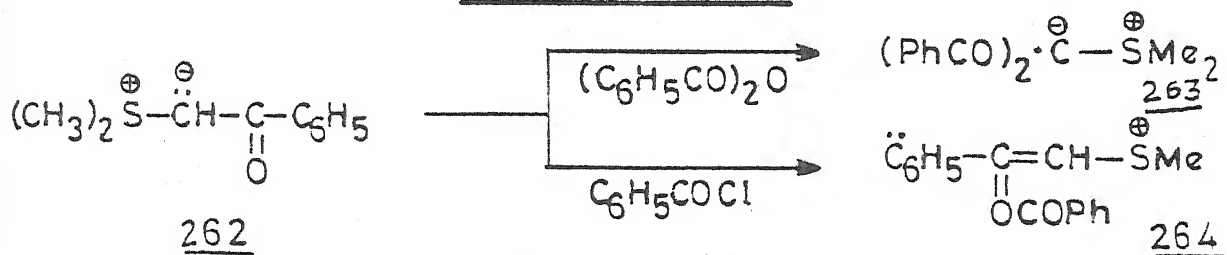
Scheme 1.103



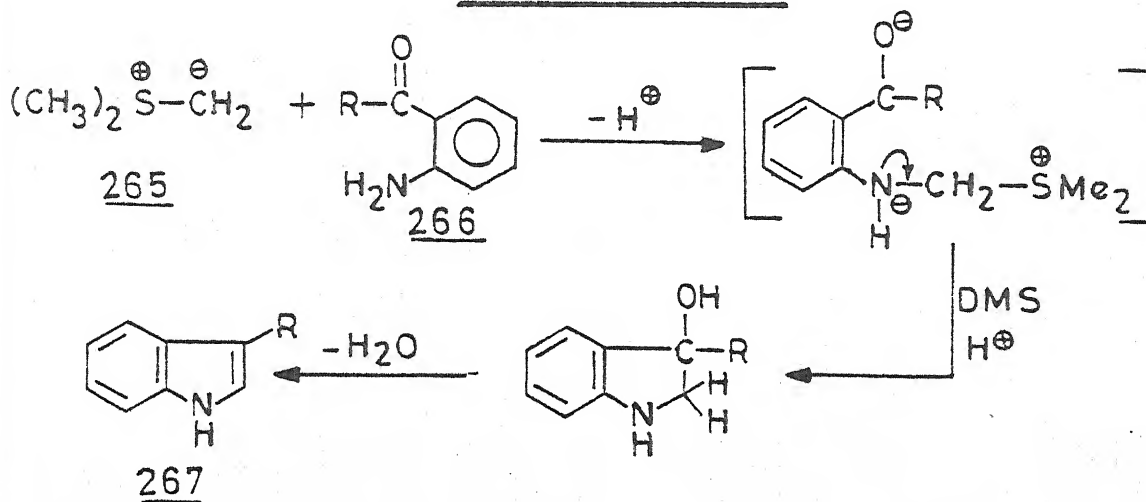
Scheme 1.104



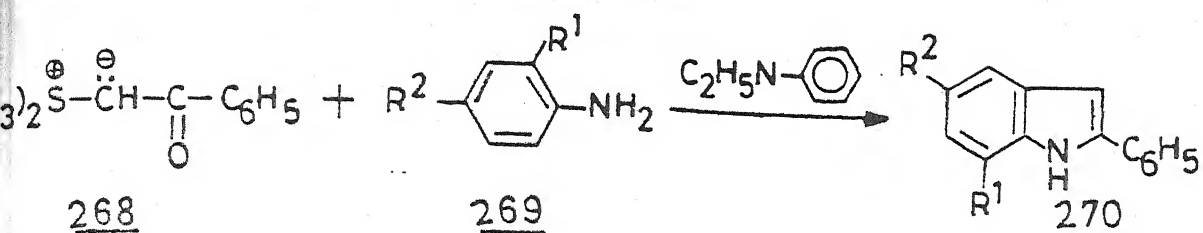
Scheme 1.105



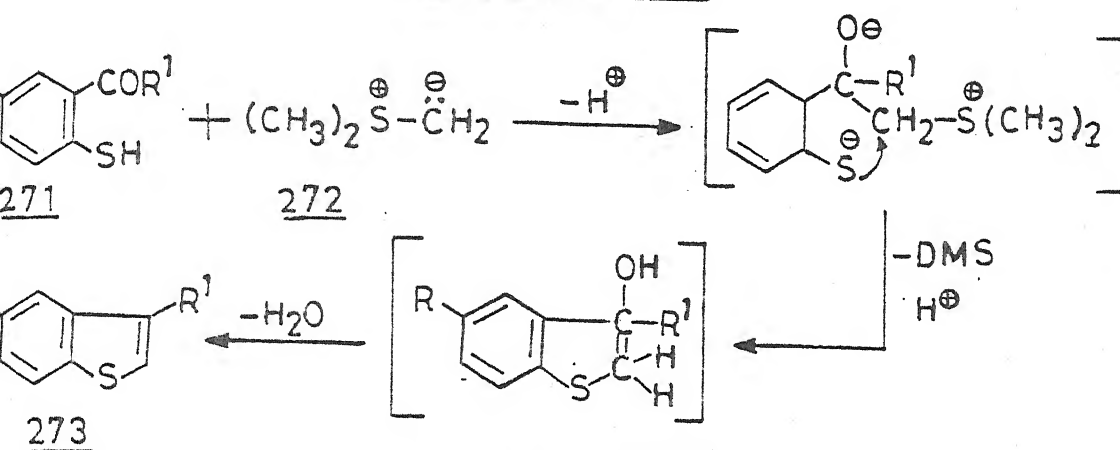
Scheme 1.106



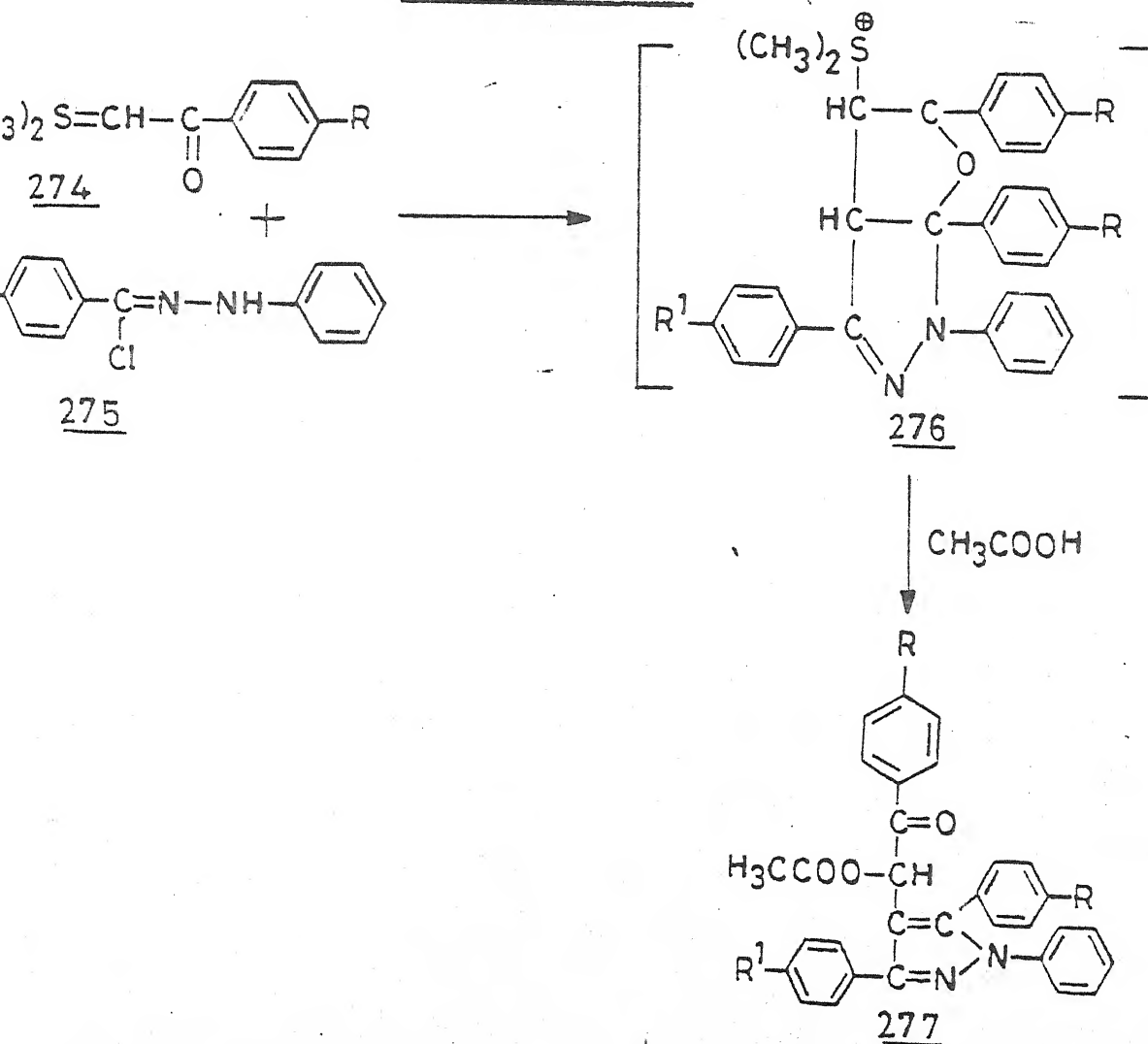
Scheme 1.107



Scheme 1.108



Scheme 1.109



pyrazole (277) via the intermediacy of a cyclic product (276) (Scheme I.109).

(J) with Multiple bonds :

(i) with C = O double bond : The most well known example²⁰¹ of sulfonium ylides, which has gained considerable importance in synthetic organic chemistry, is the epoxidation reaction which involves the condensation of sulfonium ylides (278) with carbonyl compounds (279) to form oxiranes as the exclusive products. In the reaction, a betaine type of compound (280) is formed as the intermediate product. It (280) is formed by the nucleophilic attack of the ylidic carbanion on the carbonyl carbon atom and involves the displacement by oxyanion on the carbon carrying the onium group. It seems²⁵⁹ that in the case of sulfonium betaine (280), the potential S - O bond formation does not provide sufficient driving force to dictate the course of reaction (Scheme I.110).

The conjugation and stabilization afforded by the substituents (R) present on the ylidic carbon as well as on the carbonyl group (R^2 and R^3) to the incipient double bond in the transition state appears to be the rate controlling factor. In the absence of such stabilization, oxirane formation may easily be the normal product of reaction as observed in the case of methylides.²⁶⁰

Non - stabilized sulfonium ylides e. g. methylenedimethylsulfurane (282) reacts with carbonyl compounds (183) such as benzaldehyde, cyclohexanone and benzophenone to form epoxides in fair to good yields (Scheme I.111). Frazer et al²³³ extended the study of the reaction to α, β -unsaturated ketones. They have established that methyl transfer reaction takes place at the C = C bond and not at C = O bonds as obvious from the formation of epoxides and non - isolability of cyclopropanes.

Later, Johnson et al^{324,261} studied the reaction of substituted benzyldine- phenylsulfuranes (285) with carbonyl compounds (286) which lead to the formation of epoxides exclusively (Scheme I.112). These investigations revealed that in λ -sulfuranes, unlike arsonium ylides,²⁶² the course of reaction with carbonyl compounds is not affected by the nature of the group present on the benzylic position of the ylidic carbanion. Consequently, these ylides²⁶³ are employed for the synthesis of nitro - substituted stilbene oxides which can not be prepared from their arsonium counterparts on account of the fact that the nitro group makes the reaction to proceed in the direction of olefin formation.

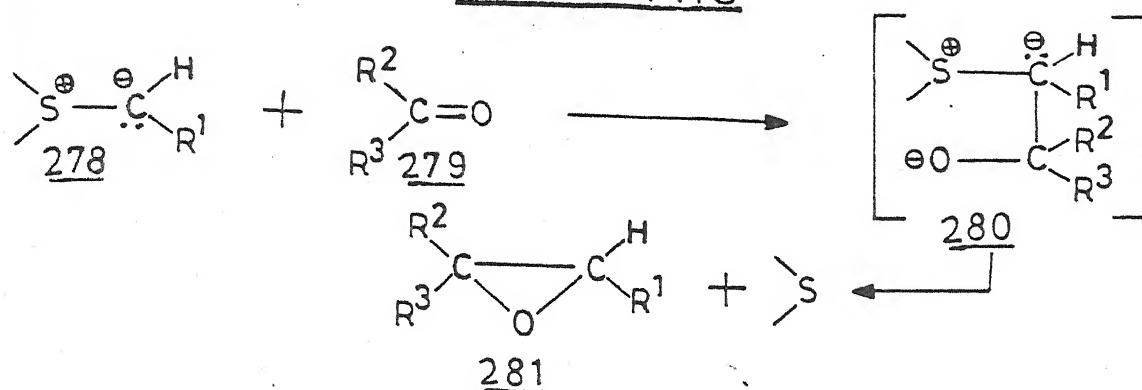
Unlike non - stabilized sulfonium ylides,

stabilized sulfonium ylides²²⁶ do not react with carbonyl functions. This non - reactivity towards carbonyl function is attributed to the diminished nucleophilicity of these ylides. However, Johnson and Lacount were able to react stabilized sulfonium ylide fluorenyllidene - dimethyl-sulfurane (288) and benzaldehyde (289) to form epoxide as the exclusive product (Scheme I.113). Soon after, Payne et al²⁶⁴ established that the stabilized ylides could be made to react with carbonyl group if it is in conjugation with a highly electropositive group. Under the conditions, the electrophilic character of the carbonyl carbon atom is enhanced resulting in its entering into reaction with stabilized sulfonium ylides.

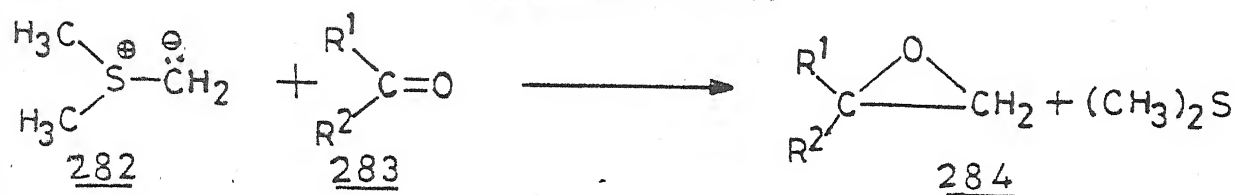
(ii) With C = C double bond : Taking a cue from the ability of the sulfonium ylides²⁰¹ to act as versatile methylene transfer reagents as shown by the fact that they form epoxides on their reaction with the carbonyl group, organic chemists went on to explore the reactivity of these ylides towards the C = C bond.

Among the first attempts was that of Corey et al^{195,199} which involved the nucleophilic addition of dimethyl-oxosulfoniummethyllide (291) with chalcone (292) to form trans 1 - benzoyl - 2 - phenylcyclopropane (293) (Scheme I.114). Such cyclopropanation reactions of sulfonium salts (294) to

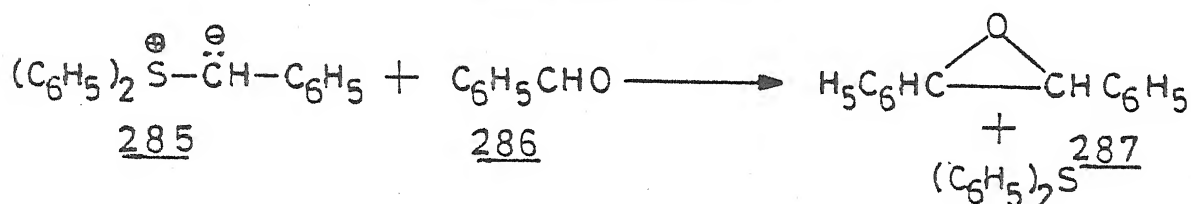
Scheme 1.110



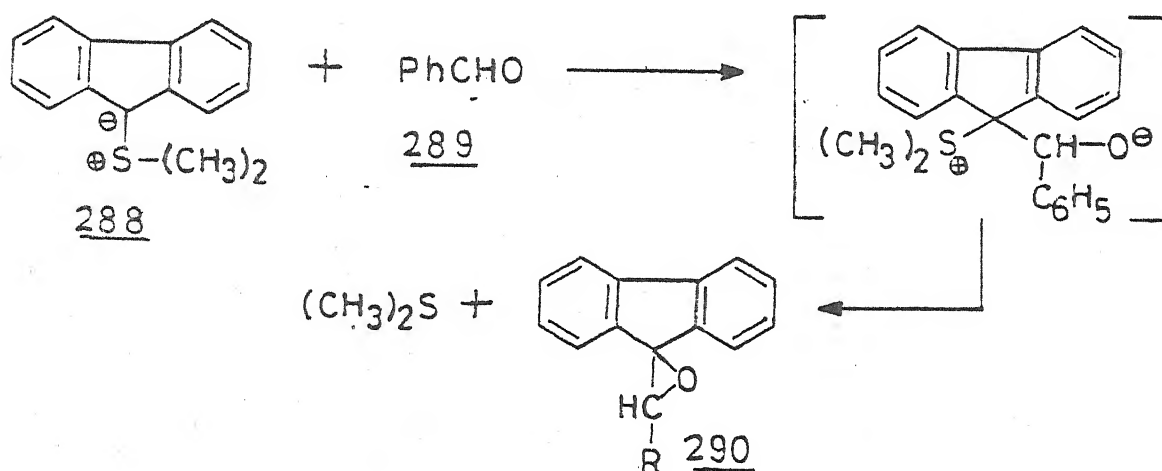
Scheme 1.111



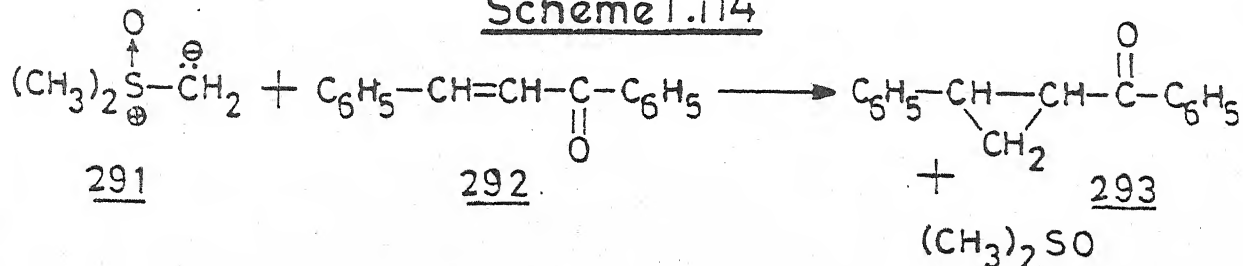
Scheme 1.112



Scheme 1.113



Scheme 1.114



form 1,2,3 tribenzoylcyclopropane (297) were known earlier.²⁶⁵ But the mechanism was not clear. It was only in 1966-67 that Trost²⁵⁰⁻²⁵¹ established that the reaction proceeded by the addition of dimethylsulfonium-phenacylide (295) to dibenzoylethylene (Scheme I.115). But the extent of nucleophilic character of the ylide carbanion determines the ease with which this reaction takes place. Thus, non - stabilized sulfonium ylides readily attack C = C bond due to greater nucleophilicity while stabilized sulfonium ylides, being less nucleophilic, attack C = C systems only if they are conjugated.

Later, Payne²⁶⁶ by studying the addition of carbethoxydimethylsulfonium ylide (298) to hexanone (299) to form cyclopropane (300), has shown that nucleophilic methylene transfer takes place at the α, β double bond and not the carbonyl group (Scheme I.116). Thus, cyclopropanated steroids²⁶⁷ and nucleosides²⁶⁸ could be synthesised.

(iii) With C = N double bond : The reaction of the non - stabilized sulfonium ylide, methylenedimethylsulfurane (301) with Schiff's bases (302) to form a variety of aziridines (303) (Scheme I.117) was studied by Frazer¹⁹⁸ and Corey.¹⁹⁹ Hoffman et al²⁶⁹ were able to show that the same ylide (301) can attack other

C = N bond systems by synthesising 1 - azabicyclobutanes (305) by the direct condensation of the ylide with aziridines (304) (Scheme I.118).

On the other hand, stabilized sulfonium ylides follow a different course of reaction with Schiff's bases. Tung et al²²⁸ reacted stabilized ylides (306) with Schiff's bases to yield aminocinnamals (308) and not aziridines (Scheme I.119).

(iv) With C = S double bond : Corey and coworkers¹⁹⁹ reacted methylene - dimethylsulfurane (309) with benzo - thiophenone (310) to form thiooxirane (311) in which the methylene transfer is effected at C = S bond (Scheme I.120).

(v) With N = S double bond : Nitroso compounds react with sulfonium ylides to form C = N bond. Johnson²³¹ has shown that it was fairly an addition - elimination - methylene transfer reaction of sulfonium ylides to produce oximes. Thus, fluorenylidenedimethylsulfurane (312) and nitrosobenzene undergo an exothermic rapid reaction to form the nitron, N - phenylfluorenoneketoxime (314) (Scheme I.121).

(K) Metalation :

Only preliminary studies²⁰⁴ have been made on the

reaction of sulfonium ylides with metal ions. It has been shown that these ylides (315) are co-ordinatively unsaturated and serve as fairly good ligands for transition metal ions (316) to form sufficiently stable metal complexes (317) (Scheme I.122).

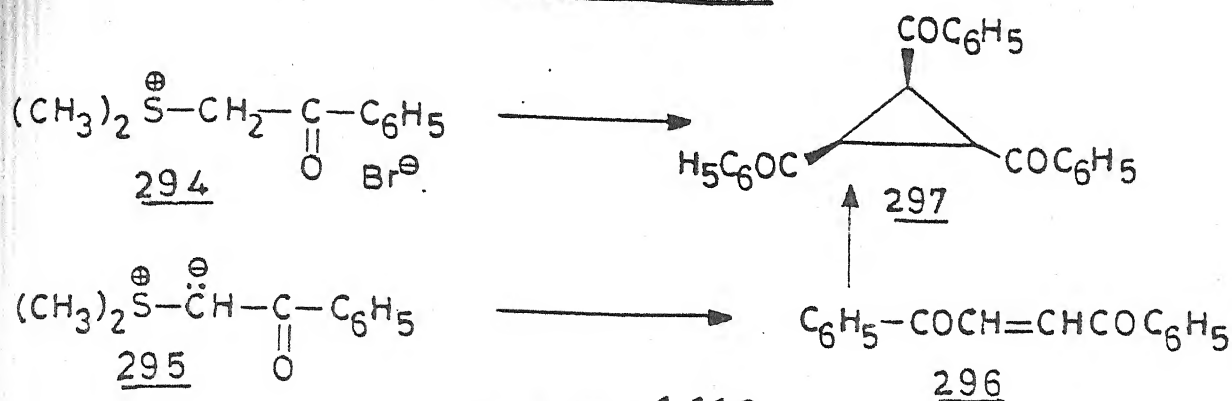
(L) α - elimination :

Very little work²⁷⁰ has been done on α - elimination. Dimethylphenacylide (318) is reported to add to cyclohexene (319) in presence of copper sulphate through α - elimination to yield cyclopropane derivative (320) in low yields²⁵⁰ (Scheme I.123). This reaction appears to proceed via the intermediacy of a copper complexed carbene.²⁷¹ Other claims of α - elimination are yet to be confirmed.

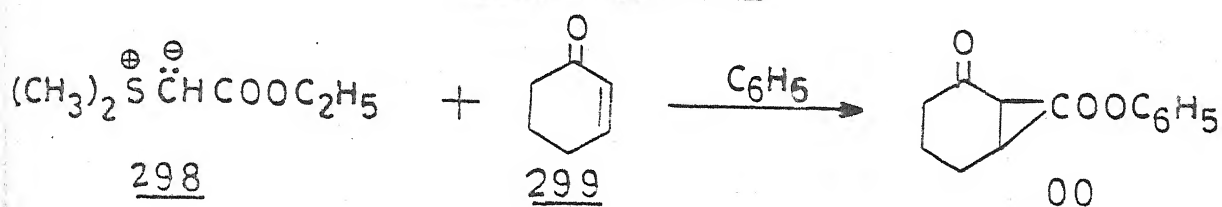
(M) Rearrangements :

Sulfonium ylides are reported to undergo various types of rearrangements. Thus, Thomson et al²⁷² have reported that benzylmethylphenacyl - sulfonium bromide (321) undergoes Steven's rearrangement to form the product (323) in which phenacylidene - benzylmethylsulfurane (322) is formed as an intermediate product (Scheme I.124). Houser and coworkers²⁷³ have shown that benzyldimethylsulfonium ion (324) in presence of amide ion undergoes Sommetel rearrangement to form O - methylbenzylmethyl sulfide (325)

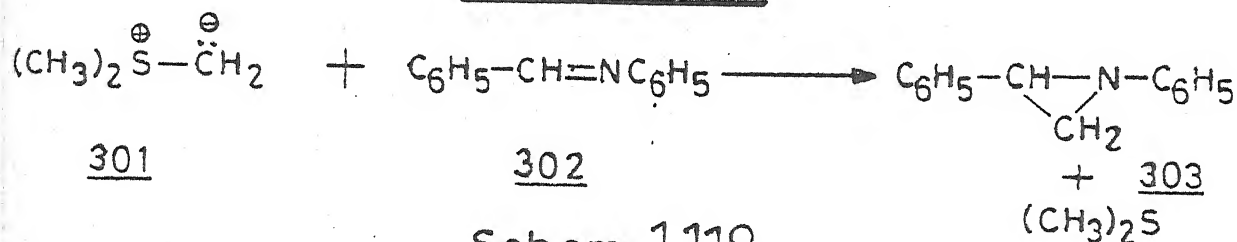
Scheme 1.115



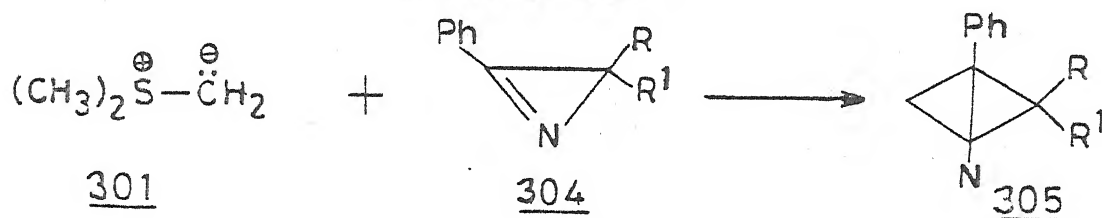
Scheme 1.116



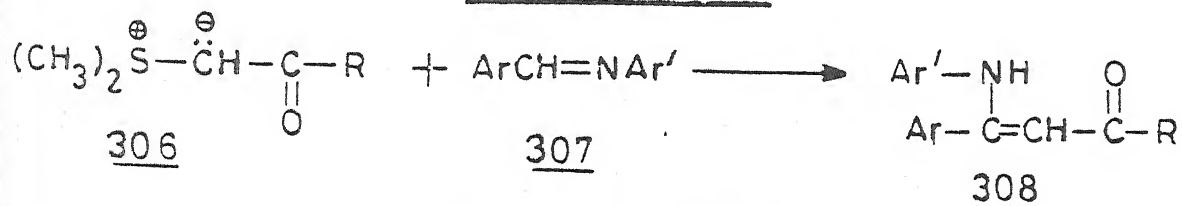
Scheme 1.117



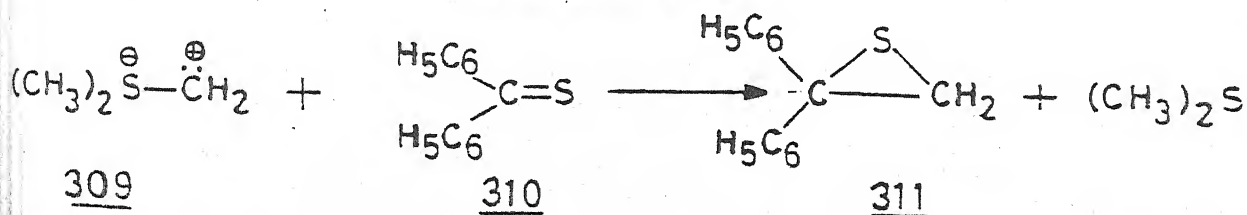
Scheme 1.118



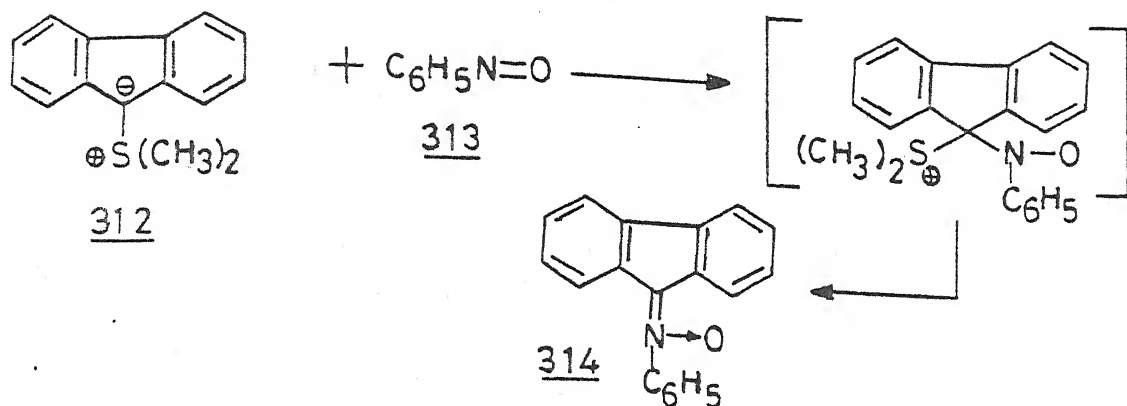
Scheme 1.119



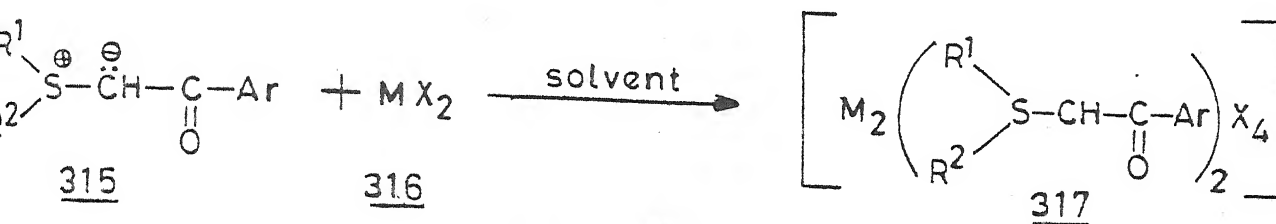
Scheme 1.120



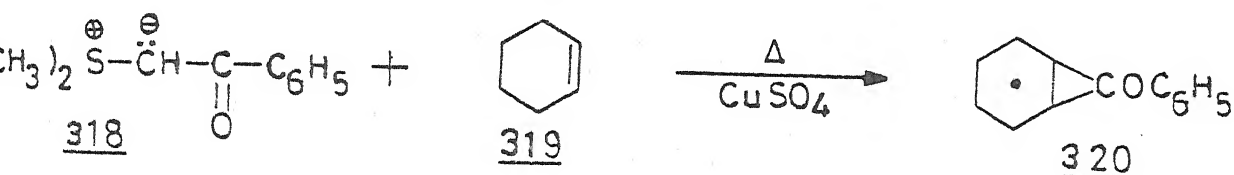
Scheme 1.121



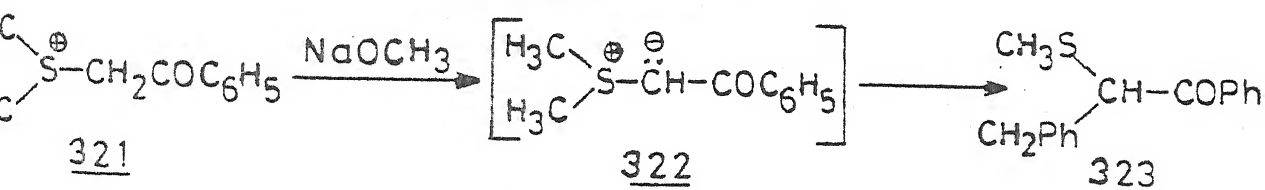
Scheme 1.122



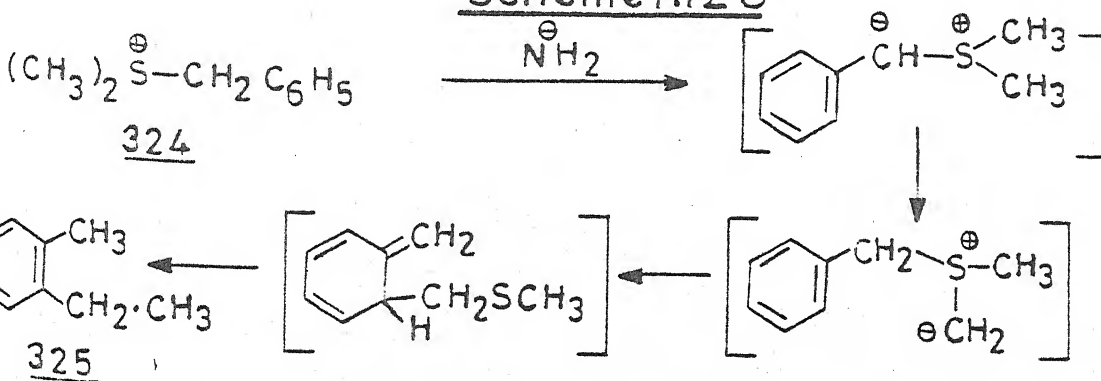
Scheme 1.123



Scheme 1.124



Scheme 1.125



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(Scheme 1.125).

These rearrangement reactions have shown great potential in the synthesis of natural products and other classes of compounds.²⁴⁰⁻²⁷⁴

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CHAPTER - II

REACTIONS OF 4 - BROMOPHENACYL - CYLOIMMONIUM,
TRIPHENYLPHOSPHONIUM AND DIMETHYLSULFONIUM YLIDES
WITH α, β - UNSATURATED KETONES : SYNTHESIS OF
SYMMETRICAL AND ASYMMETRICAL 2,4,6 - TRIARYLPYRIDINES

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REACTIONS OF 4 - BROMOPHENACYL - CYCLOIMMONIUM O,
TRIPHENYLPHOSPHONIUM AND DIMETHYLSULFONIUM YLIDES
WITH α, β - UNSATURATED KETONES : SYNTHESIS OF
SYMMETRICAL AND ASYMMETRICAL 2,4,6 - TRIARYLPYRIDINES

2.1. ABSTRACT :

4 - Bromopyridinium bromide, 4- bromophenacyltriphenylphosphonium bromide and 4 - bromophenacyldimethylsulfonium bromide have been prepared by the reaction of 4 - bromophenacyl bromide with pyridine, triphenylphosphine and dimethylsulfide respectively in benzene at reflux temperature to give fair to good yields. These ylides react separately with mono- and disubstituted benzylideneacetophenone in presence of ammonium acetate in glacial acetic acid or methanol to form asymmetrical pyridines having different substituents at 2,4 and 6 positions in each case in varying yields (40-70%). When these ylides were coupled with substituted benzylidene - 4 - bromoacetophenone, 2,6 (4 - bromophenacyl) - 4 substituted phenylpyridines i.e. symmetrical pyridines having identical substituents were formed in good yields (50-70%). Attempts to synthesise fully symmetrical pyridines having identical substituents at 2,4 and 6 positions involved the condensation of 4 - bromobenzilidene ylides with 4 - bromobenzilidene - 4 - bromoacetophenone in ammonium acetate.

The reactivity was found to be maximum in the

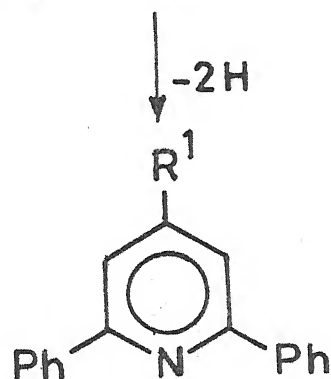
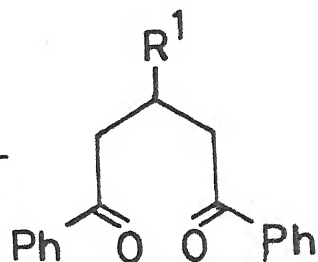
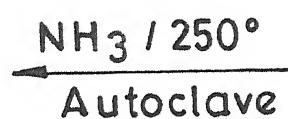
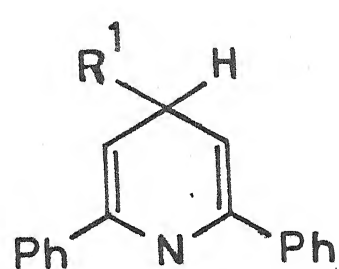
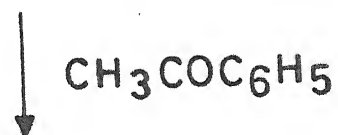
case of cycloimmonium ylides and the least in the case of phosphonium ylides as evident from the yields of pyridine in the respective cases. The structures of products were elucidated on the basis of elemental, IR and NMR spectra.

2.2. INTRODUCTION :

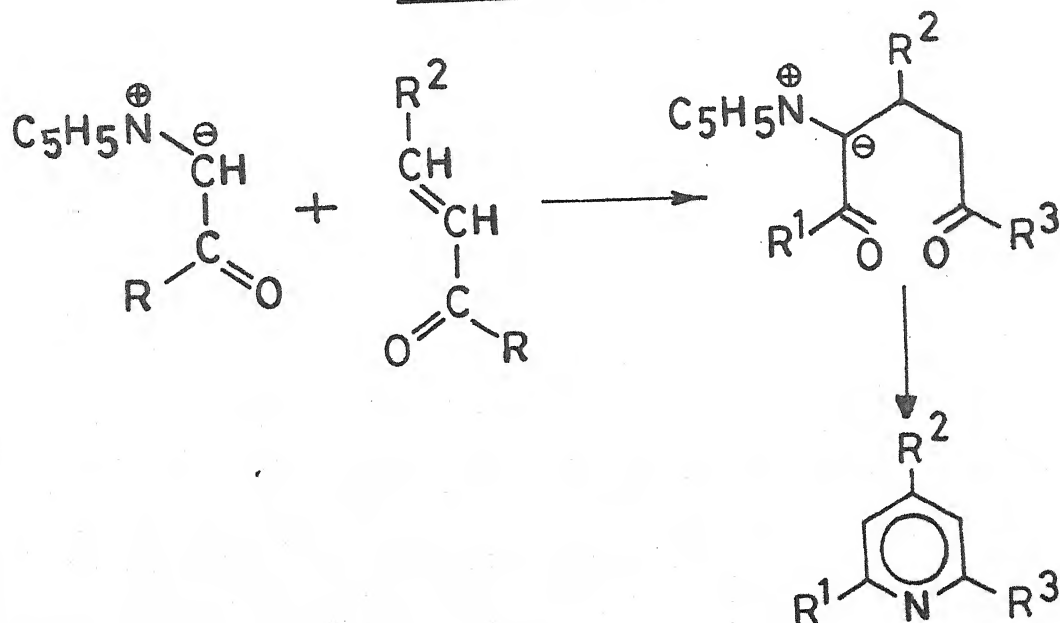
One of the earliest methods involving aza ring closure leading to the synthesis of substituted pyridines was reported by Tschitschibabin.¹ The method involves the condensation of aldehyde and methylketone in presence of liquid ammonia (Scheme II.1). But this route was not versatile because it requires harsh reaction conditions and gave poor yields of pyridines. Subsequent to this report, Frank et al^{2,3} made an improvement using ammonia and catalytic amounts of ammonium acetate.

Later Krohnke et al^{4,5} developed a superior method for the synthesis of pyridines. This method involves the interaction of pyridinium salts or ylides with α, β - unsaturated ketones (Scheme II.2). The course of the reaction involves the same pentane - 1,5 - dionyl intermediate analogous to the diketone intermediate formed in the earlier methods. The intermediate undergoes aza ring closure with ammonium acetate in glacial acetic acid to give 2,4,6 - triarylpyridines. The superiority of Krohnke^{4,5} method over that of Tschitschibabin¹ lies in the requirement^{of} mild

Scheme II-1



Scheme II-2



reaction conditions and better yields of pyridines. Moreover, earlier methods^{1,3} were restricted to the preparation of symmetrical pyridines having identical substituents at 2 and 6 positions of the pyridine ring. The Krohnke's method allows the synthesis of both symmetrical and asymmetrical pyridines. The latter have different substituents at 2,4 and 6 positions of the pyridine nucleus.

In the recent years, analogous phosphonium⁶, Sulfonium⁷ and arsonium⁸ salts have also been used in the synthesis of 2,4,6 - triarylpyridines. The reaction in each case involves coupling of triphenylphosphonium, sulfonium and arsonium salts with α, β - unsaturated ketones in presence of ammonium acetate in acetic acid.

In the present chapter, the synthesis of some new asymmetric and symmetrical bromopyridines by the condensation of 4 - bromophenacylpyridinium, 4 - bromophenacyltriphenylphosphonium and 4 - bromophenacyldimethylsulfonium bromide with a wide range of benzylacetophenones has been reported. The investigations were undertaken with a view to compare and test the domain of synthetic potentialities of these ylides.

2.3. RESULTS AND DISCUSSION :

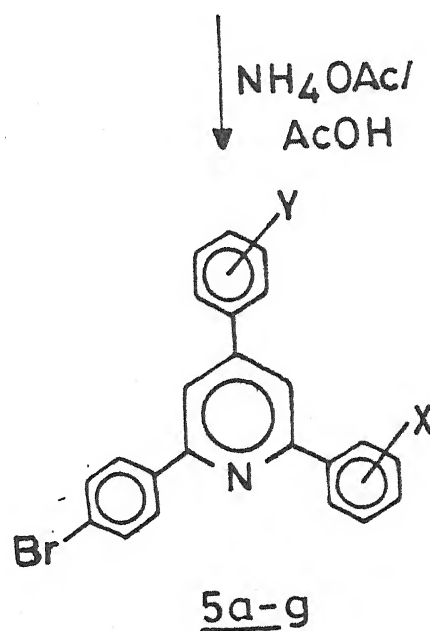
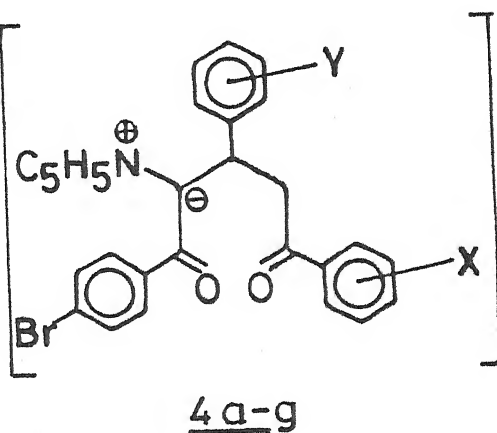
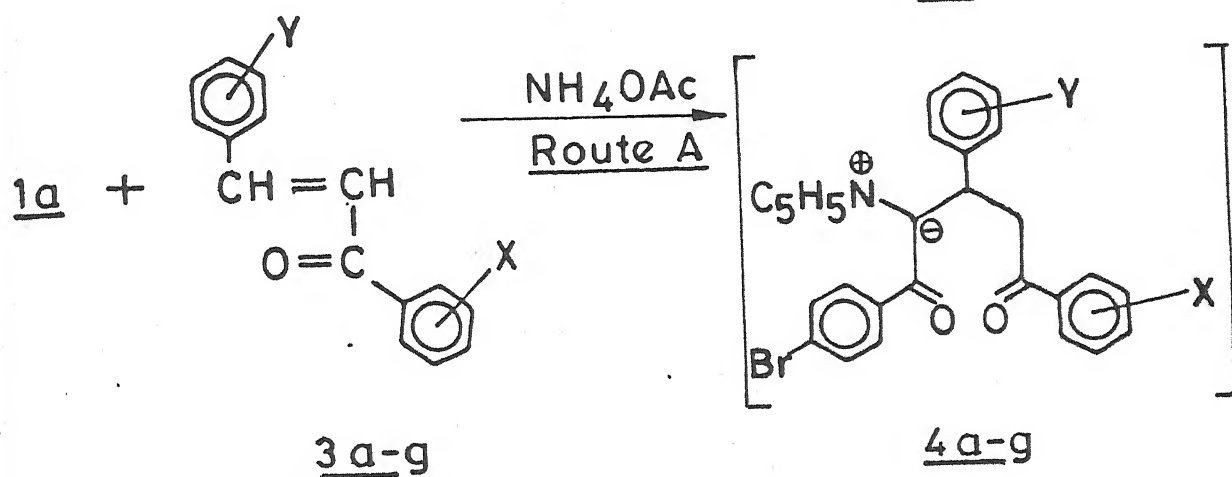
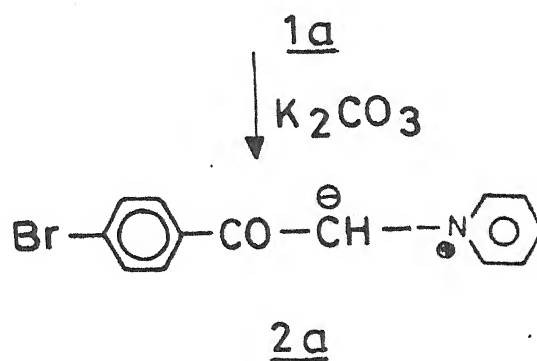
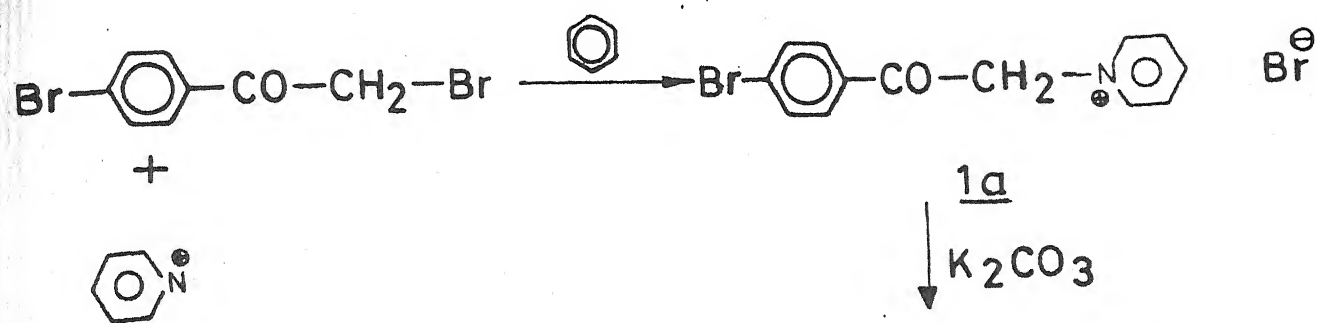
The reaction of pyridine with 4 - bromophenacyl bromide in benzene or THF at reflux temperature gave

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4 - bromophenacylpyridinium bromide (1a). The treatment of salt (1a) with aqueous K_2CO_3 gave 4 - bromophenacylidine ~~pyridinium~~ ylide (2a) which was isolable but not storable due to sensitivity towards atmospheric components. Therefore, the reaction was carried out by generating the ylide (2a) in situ from its corresponding precursor salt (1a). The structure of salt (1a) was established by comparison of its melting point with that reported in literature. The IR spectrum of the salt revealed a characteristic absorption band at 1690 cm^{-1} due to C - O stretching vibrations for the carbonyl group. The diagnostic absorption band at 3300 cm^{-1} was observed due to C - H stretching frequency of methylene group attached to the nitrogen atom. The NMR spectrum of the salt (1a) displayed a peak at δ 6.80 (singlet) due to the of methylene group. Other aromatic protons were exhibited in the range of δ 7.20 - 8.40 (multiplet). The reaction of salt (1a) or ylide (2a) with substituted benzylideneacetophenones (3a-g) in presence of ammonium acetate and glacial acetic acid at reflux temperature gave asymmetrical 2 -(4 - bromophenyl)-4,6 di (substituted phenyl) pyridines (5a-g) (Scheme 11.3) (Route A).

On similar lines, symmetrical pyridines 2,6-di (4 - bromophenyl)-4- substitutedaryl pyridines (5h-k) were prepared by the reaction of the salt (1a) with benzylidene-4- bromoacetophenone (3h-3k) in a mixture of ammonium acetate

Scheme II-3

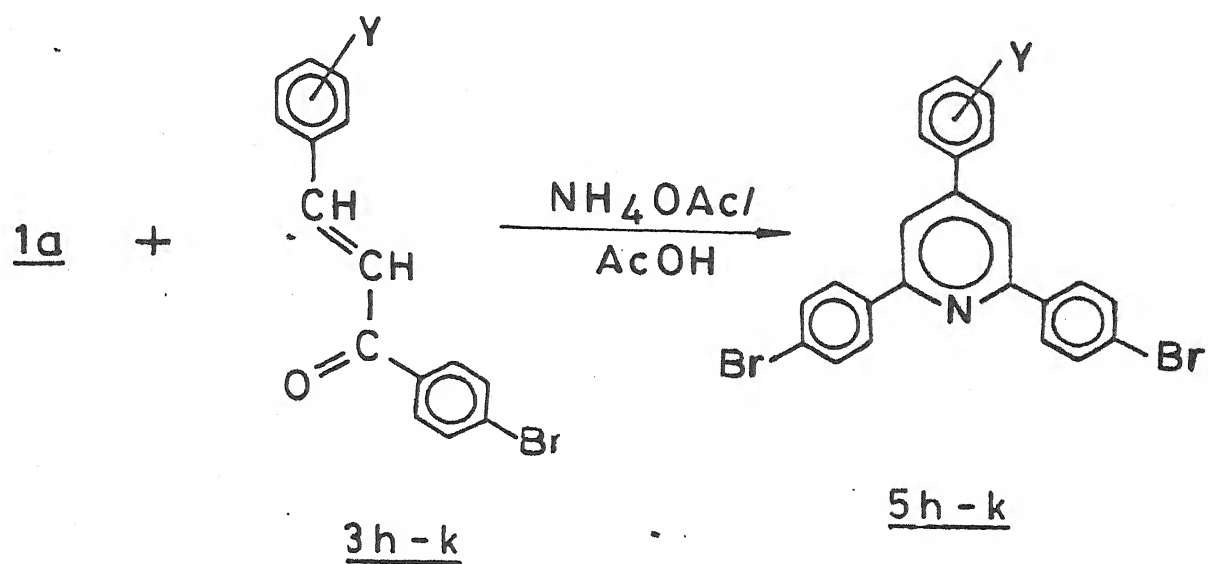


and acetic acid (Scheme II.4).

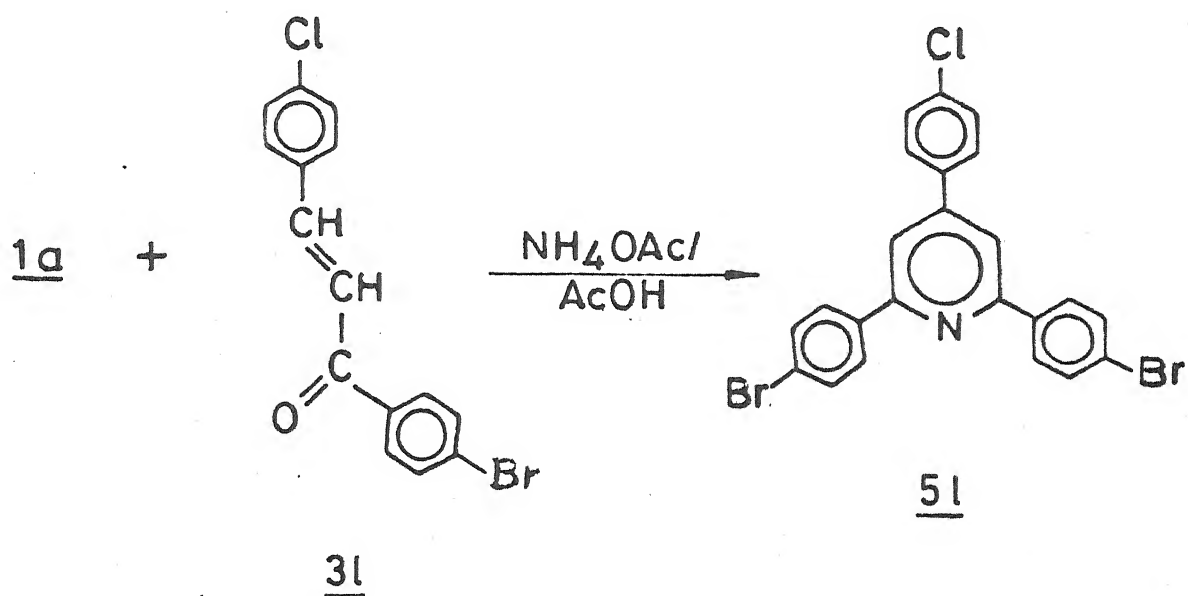
Attention was then directed towards the pyridine (51) having identical groups at 2,4 and 6 positions of the pyridine nucleus. This was achieved by heating the salt (1a) with 4 - bromobenzilidene - 4 - bromoacetophenone (31) in presence of acetic acid (Scheme II.5).

The reaction of triphenylphosphine with 4 - bromophenacyl bromide in benzene or THF at reflux temperature leads to the formation of 4 - bromophenacyltriphenylphosphonium bromide (1'a). The treatment of the salt (1'a) with alcoholic sodium ethoxide furnished 4 - bromophenacyltriphenylphosphonium ylide (2'a) which could be isolated but could not be stored due to its sensitivity towards the atmospheric components. Therefore, the reaction was carried out by generating the ylide in situ (2'a) from its, corresponding precursor salt (1'a). The structure of the salt (1'a) was established by the comparison of its melting point with that reported in literature. The IR spectrum of the phosphonium salt(1'a) revealed a characteristic absorption band at $1665 - 85 \text{ cm}^{-1}$ due to C - O stretching vibrations for the carbonyl group. The diagnostic absorption band at 3275 cm^{-1} was observed due to the C - H stretching frequency of the methylene group attached to the phosphorus atom. The NMR spectrum of the salt displayed a peak δ 6.80 (singlet) due to the methylene group. Other aromatic protons

Scheme II.4



Scheme II.5



were displayed in the range δ 7.36 - 8.20 (multiplet).

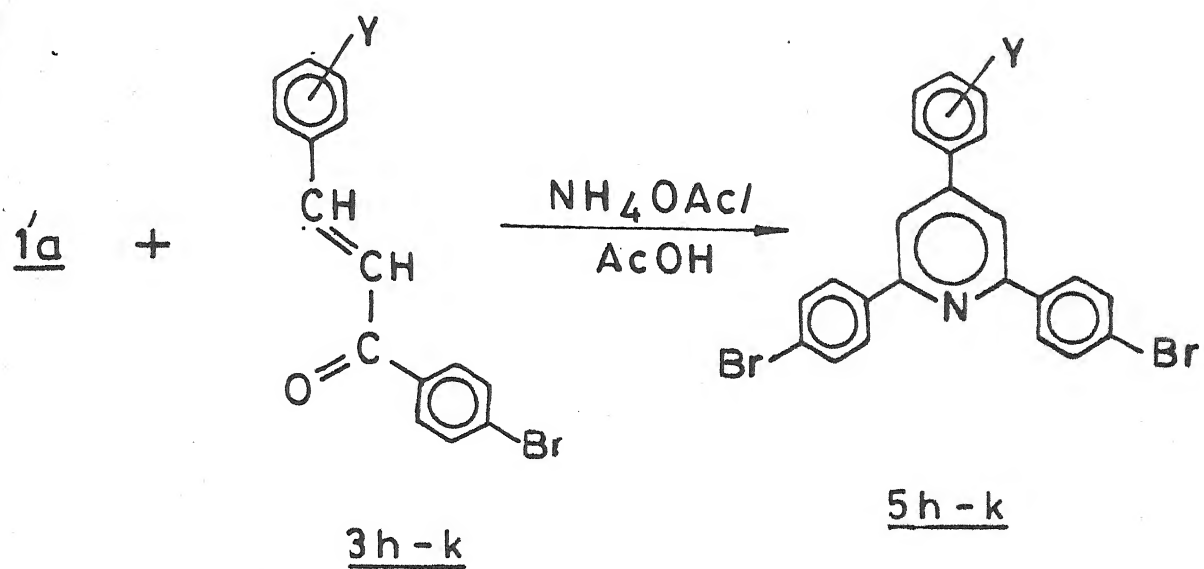
The reaction of the salt (1'a) with substituted benzylideneacetophenones (3a-g) in presence of ammonium acetate and glacial acetic acid gave asymmetric 2 - (4 - bromophenyl) - 4,6 - di (substituted phenyl) pyridines (5a-g) (Scheme II.6) (Route B).

Quite similarly, symmetrical pyridines 2,6 - di (4 - bromophenyl) - 4 - substituted aryl pyridines (5h-k) were prepared by the reaction of the salt (1'a) with benzilidene - 4 - fluoroacetophenone (3h-k) with a mixture of ammonium acetate and acetic acid (Scheme II.7).

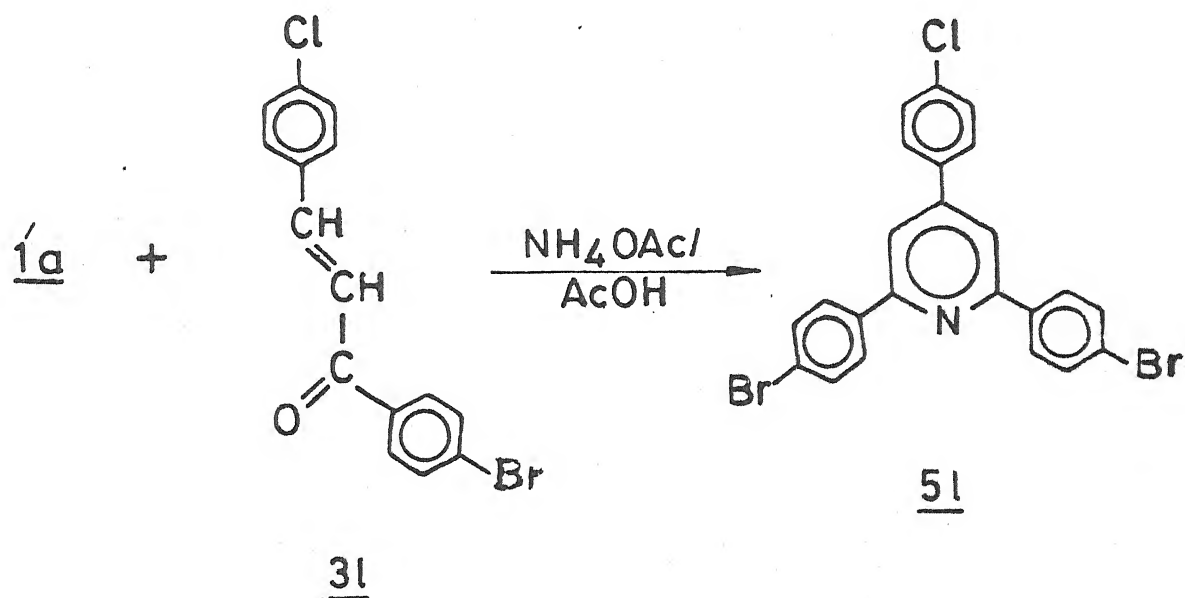
The synthesis of pyridine (5l) having identical groups at 2,4 and 6 positions of the pyridine nucleus was achieved by heating the salt (1'a) with 4-bromobenzylidene - 4 - bromoacetophenone (3l) in the presence of ammonium acetate in acetic acid (Scheme II.8).

Finally, the reaction of dimethylsulfide with 4 - bromophenacyl bromide in benzene or THF at reflux temperature gave 4 - bromophenacyldimethylsulfonium bromide (1''a). The treatment of the salt (1''a) with aqueous K_2CO_3 or NaOH gave 4 - bromophenacylsulfonium ylide (2''a) which could be isolated. But it could not be stored due to its sensitivity towards atmospheric components. The reaction was, therefore, carried out in situ by generating the ylide

Scheme II.7



Scheme II.8



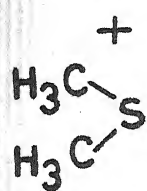
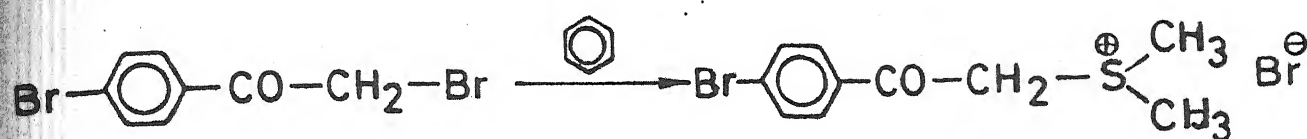
from its corresponding precursor salt (1^a) whose structure was evidenced by the comparison of its melting point with that reported in literature. The IR spectrum of the sulfonium salt (1^a) revealed a characteristic absorption band at 1675 cm^{-1} due to C = O stretching vibrations of the carbonyl group. The diagnostic absorption band at 3250 cm^{-1} was observed due to the C - H stretching frequency of the methylene group directly attached to the sulfonium group. The NMR spectrum of the salt (1^a) showed a peak at δ 4.45 (singlet) due to methylene protons. Other aromatic protons were exhibited in range δ 7.25 - 7.86 (multiplet).

The reaction of the salt (1^a) with substituted benzylideneacetophenones (3a-g) in presence of ammonium acetate and acetic acid at reflux temperature resulted in the formation of asymmetrical 2 - (4 - bromophenyl) -4,6 - di (substituted phenyl) pyridines (5a-g) (Scheme II.9) (Route C).

Similarly, symmetrical pyridines 2,6 - di (4 - bromophenyl) - 4 - substituted arylpyridines (5h-k) were prepared by the reaction of the salt (1^b) with benzylidene - 4 - fluoroacetophenones (3h-k) in a mixture of ammonium acetate and acetic acid (Scheme II.10).

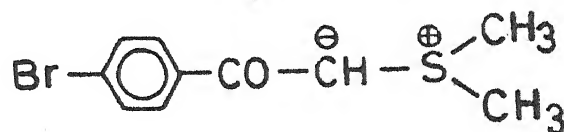
The synthesis of fully symmetrical pyridine (5l) having identical groups at 2,4 and 6 positions of the

Scheme II.9

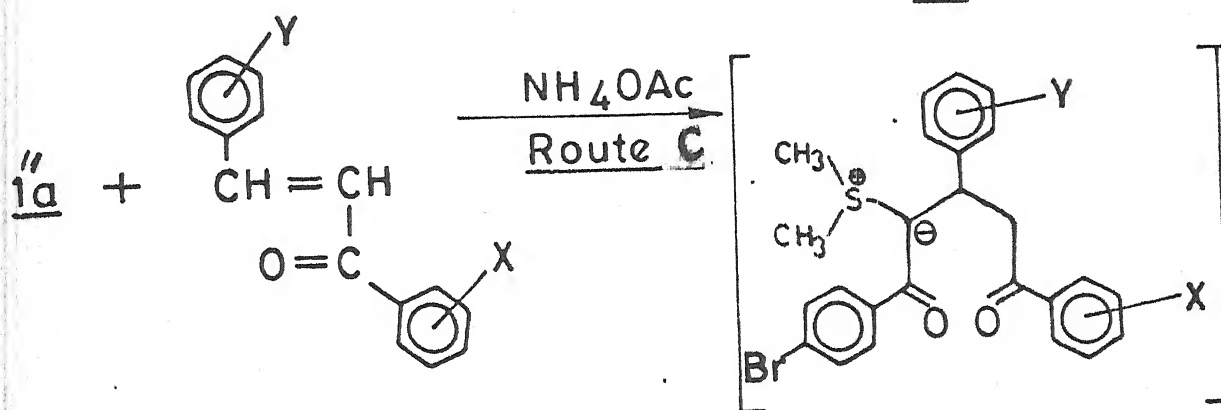


1a

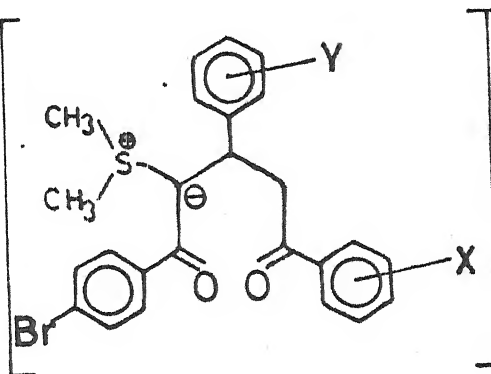
$\downarrow \text{K}_2\text{CO}_3$



2a

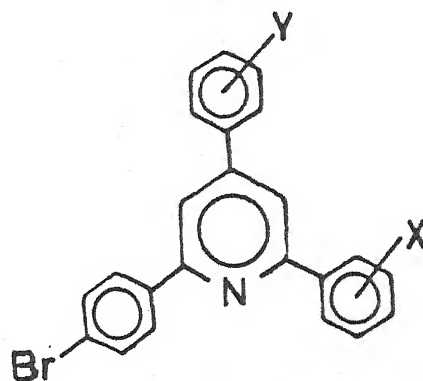


3a-g



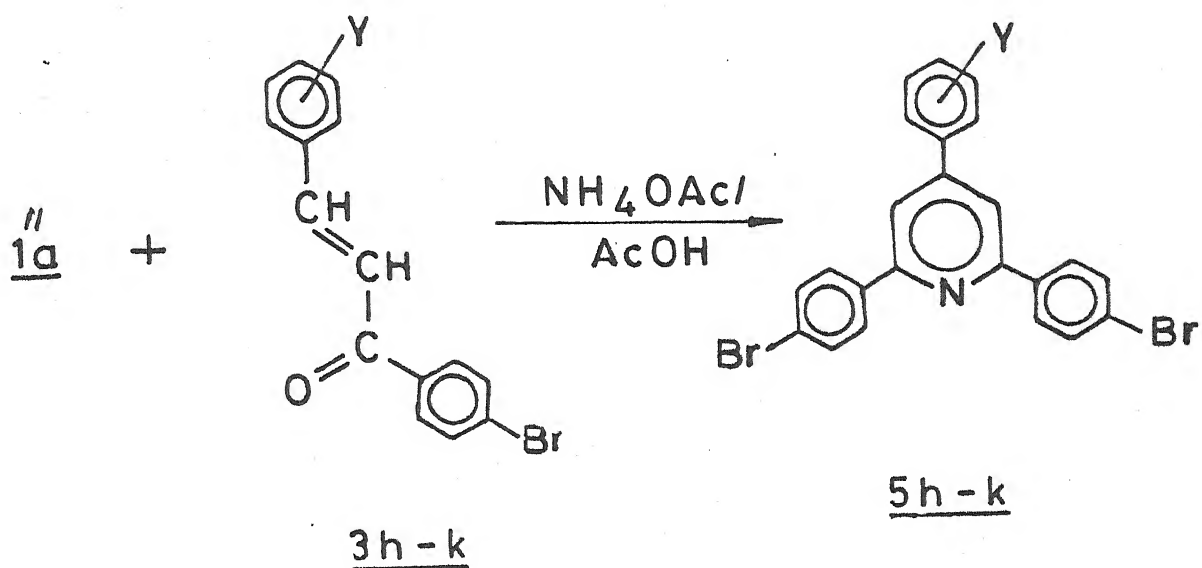
4a-g

$\downarrow \text{NH}_4\text{OAc} / \text{AcOH}$

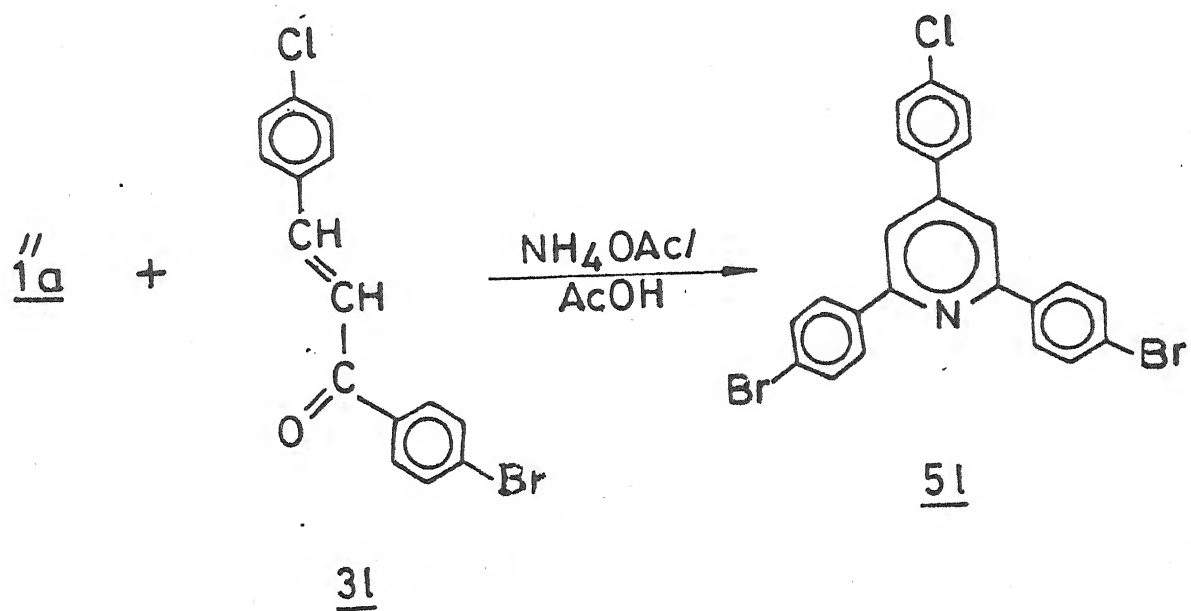


5a-g

Scheme II.10



Scheme II.11



pyridine nucleus was brought about by heating the salt (1^a) with 4 - bromobenzylidene - 4 - bromoacetophenone (31) in presence of ammonium acetate and acetic acid (Scheme II.11).

In all the cases, the reaction appears to proceed by the attack of the ylide (2a, 2^a or 2^a) on the β -carbon of the α, β -unsaturated ketone (3) to form (pentane - 1,5-dionyl) pyridinium/phosphonium/sulfonium intermediates (4a-1/4^a-1/4^a-1) which, in turn, undergo aza ring closure in presence of ammonium acetate to form 2,4,6 - triarylpyridines.

The new bromopyridines (5a-1) synthesized by using cycloismonium ylides (Route A), phosphonium ylides (Route B) and sulfonium ylides (Route C) are listed in table II.1.

All the pyridines gave satisfactory elemental analysis. The spectral data confirmed the proposed structures of the pyridines. The IR spectra showed characteristic absorption bands in the region $3150 - 3000 \text{ cm}^{-1}$ which were assigned to C - H stretching mode of the pyridine ring. Two bands in the region of 1000 cm^{-1} and 1500 cm^{-1} were due to interactions between C = H and C = N vibrations of the pyridine ring⁹⁻¹⁰. The NMR spectra of the pyridines showed two pyridyl protons in the range δ 6.40 - 6.65 and aromatic protons in the region δ 6.40 - 8.35 (Tables II.2 and II.3).

On the basis of the investigations carried out in the field in the present work, some empirical generalisations

can now be made as to the comparative reactivity and stability of the cycloimmonium, phosphonium and sulfonium ylides. The yields of the corresponding pyridines may be used to characterise the order of reactivity as cycloimmonium ylides $>$ Δ -sulfuranes $>$ phosphonium ylides.

The greater reactivity of the cycloimmonium ylides than the corresponding phosphonium and sulfonium analogues may be attributed to the former's enhanced nucleophilicity due to lack of $d\pi - p\pi$ bonding. In the case of Δ -sulfuranes and phosphonium ylides, $d\pi - p\pi$ bonding favours ylene form resulting in lesser ylidic character and lower nucleophilicity and hence lesser yields of pyridines.

Both sulfonium and phosphonium ylides have $d\pi - p\pi$ bonding. Of the two, Δ -sulfuranes are more reactive because the presence of two methyl groups makes them more nucleophilic compared to phosphonium ylides which have three phenyl groups and hence are characterised by lesser nucleophilicity. This may probably be attributed to comparatively greater resonance stabilization caused by the three phenyl groups and greater steric hinderance offered by them.

2.4. EXPERIMENTAL :

2.4.1. GENERAL TECHNIQUES :

Unless and until stated otherwise, the melting

points were recorded in degrees centigrade on a Gallen Kamp apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer infracord spectrophotometer using KBr phase. Varian A-60 and A-100 spectrometers were used to record NMR spectra with tetramethylsilane (TMS) as an internal standard. The products were separated and purified by column chromatography using neutral alumina as the absorbent. Glass microscope slides coated with silica gel G were used for thin layer chromatography (TLC). The spots on the slides were developed by placing them in an iodine chamber.

2.4.2. STARTING MATERIALS :

All the reagents were obtained from commercial sources (E. Merck, BDH and SISCO). Starting materials were prepared according to procedures reported in literature.

I. Preparation of 4 - bromophenacylidinecycloimmonium, -triphenylphosphonium and -dimethylsulfonium salts (1a, 1'a and 1''a):

A solution of 100 m mole of 4- bromophenacyl bromide and 100 ml of pyridine, triphenylphosphine or dimethylsulfide in 100 ml of benzene or tetrahydrofuran was refluxed for 6-8 hours. The excess of the solvent was evaporated and petroleum ether was added to precipitate the salt (1a, 1'a or 1''a) which was then recrystallised from

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chloroform: petroleum ether (1 : 2).

The melting points of these salts were comparable with those reported in literature as shown below:-

Salt	m.p. °C	
	Found	Lit. Value
1 a	240 - 42	242 - 43 ¹⁰
1 ¹ a	258 - 60	258 ¹³
1 ² a	132 - 34	134 ¹²

All the substituted benzylideneacetophenones (3a-1) were prepared by the reaction of substituted benzaldehydes and substituted acetophenones in presence of alcoholic sodium hydroxide as reported in literature.

II. General procedure for the preparation of 2,4,6 - triarylpyridines :

To a stirred mixture of salt (1a, 1¹a or 1²a) (3m mole) and ammonium acetate (3g) in glacial acetic acid (25 ml), a solution of substituted benzylacetophenone(3a-1) (3m mole) dissolved in 20 ml glacial acetic acid was added drop wise by a dropping funnel at the reflux temperature in an atmosphere of nitrogen. After complete addition of the chalcone, the mixture was refluxed for 3-6 hours and then left overnight at the room temperature. The mixture was then

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poured in ice cold water (50 ml) and constantly stirred. A solid mass was precipitated. It was filtered and washed twice with water and methanol. The product, on recrystallisation, with a suitable solvent gave the titled crystalline pyridines(5a-1) in 40-80% yield as shown in table II.1.

TABLE II.1

PHYSICAL PROPERTIES OF 2, 4, 6 - TRIARYLPYRIDINES (5a - 1)

Comp- ound	X	Y	Yield %	Route used	m.p. °C	Recrystallisation solvent	Chemical analysis Found (Calculated)%	C	H	N
1	2	3	4	5	6	7	8	9	10	11
5a	H	H	60	A	156-58	C ₅ H ₅ N/MeOH	71.38	4.11	3.68	
			55	B	154-55	C ₅ H ₅ N/MeOH	71.46	4.12	3.70	
			52	C	155-56	C ₅ H ₅ N/MeOH	71.44 (71.50)	4.18 (4.15)	3.65 (3.63)	
5b	H	Cl	58	A	170-72	CHCl ₃ /MeOH	65.66	3.58	3.30	
			44	B	168-69	CHCl ₃ /MeOH	65.67	3.56	3.31	
			50	C	172-73	CHCl ₃ /MeOH	65.55 (65.64)	3.58 (3.57)	3.30 (3.32)	
5c	4-Cl	H	55	A	185-87	C ₅ H ₅ N	65.62	3.52	3.36	
			45	B	184-86	C ₅ H ₅ N	65.60	3.59	3.34	
			52	C	186-88	C ₅ H ₅ N	65.58 (65.64)	3.54 (3.57)	3.39 (3.32)	

1	2	3	4	5	6	7	8	9	10
5d	4-CH ₃	H	70	A	150-52	CHCl ₃ /MeOH	71.92	4.56	3.48
			55	B	152-53	CHCl ₃ /MeOH	71.96	4.57	3.53
			60	C	148-50	CHCl ₃ /MeOH	72.04 (72.00)	4.52 (4.50)	3.56 (3.50)
5e	4-OCH ₃	H	63	A	145-47	CHCl ₃ /MeOH	69.20	4.30	3.35
			52	B	144-46	CHCl ₃ /MeOH	69.18	4.28	3.34
			60	C	144-45	CHCl ₃ /MeOH	69.26 (69.23)	4.31 (4.33)	3.36 (3.37)
5f	H	3,4-O ₂ CH ₂	50	A	160-62	C ₅ H ₅ N/MeOH	72.30	4.00	3.50
			40	B	158-59	C ₅ H ₅ N/MeOH	72.32	4.04	3.48
			48	C	161-63	C ₅ H ₅ N/MeOH	72.28 (72.36)	4.03 (4.01)	3.47 (3.52)
5g	H	3,4-di OCH ₃	65	A	128-30	C ₅ H ₅ N/MeOH	67.24	4.45	3.10
			52	B	130-32	C ₅ H ₅ N/MeOH	67.25	4.44	3.16
			60	C	126-28	C ₅ H ₅ N/MeOH	67.29 (67.26)	4.44 (4.48)	3.12 (3.14)

1	2	3	4	5	6	7	8	9	10
5h	4-Br	H	50	A	164-65	C ₅ H ₅ N/MeOH	59.30	3.20	2.98
			45	B	165-68	C ₅ H ₅ N/MeOH	59.31	3.19	2.97
			45	C	165-67	C ₅ H ₅ N/MeOH	59.34 (59.35)	3.21 (3.23)	2.99 (3.01)
5i	4-Br	4-CH ₃	55	A	143-45	C ₅ H ₅ N/MeOH	59.32	3.22	2.98
			42	B	144-46	C ₅ H ₅ N/MeOH	59.36	3.20	3.04
			50	C	144-45	C ₅ H ₅ N/MeOH	59.30 (59.35)	3.38 (3.23)	3.00 (3.01)
5j	4-Br	4-OH ₃	50	A	178-80	C ₅ H ₅ N/MeOH	58.10	3.43	2.80
			48	B	176-78	C ₅ H ₅ N/MeOH	58.13	3.40	2.86
			48	C	177-79	C ₅ H ₅ N/MeOH	58.12 (58.15)	3.41 (3.43)	2.87 (2.83)
5k	4-Br	4-Cl	50	A	190-92	C ₂ H ₅ OH	55.20	2.76	2.79
			45	B	192-94	C ₂ H ₅ OH	55.26	2.82	2.76
			50	C	191-92	C ₂ H ₅ OH	55.21 (55.23)	2.85 (2.80)	2.83 (2.80)

1/19/11

1	2	3	4	5	6	7	8	9	10
51	4-Br	4-Br	50	A	185-86	C ₂ H ₅ OH	50.70	2.53	2.55
			45	B	184-85	C ₂ H ₅ OH	50.71	2.55	2.53
			48	C	182-84	C ₂ H ₅ OH	50.75 (50.73)	2.54 (2.57)	2.54 (2.57)

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TABLE II.2

IR SPECTRAL PROPERTIES OF 2,4,6-TRIARYLPYRIDINES

Compound	$\nu_{\text{C}-\text{N}}^{\text{aryl}}$ (cm^{-1})	$\nu_{\text{C}=\text{C}}$ (cm^{-1})	$\nu_{\text{C}=\text{N}}$ (cm^{-1})	$\phi_{\text{C}-\text{H}}$ (cm^{-1})
5a	3150	1605	1500	995
5b	3060	1600	1505	1000
5c	3115	1698	1510	998
5d	3030	1600	1508	990
5e	3000	1600	1500	1005
5f	3010	1610	1508	1010
5g	3000	1608	1500	995
5h	3070	1610	1500	992
5i	3065	1600	1510	1000
5j	3025	1602	1505	998
5k	3035	1610	1515	995
5l	3015	1600	1505	997

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TABLE II.3

NMR SPECTRAL DATA OF 2,4,6 - TRIARYLPYRIDINES¹H NMR data (CDCl₃)

Compound	δ (ppm)	No. of protons	Assignment
1	2	3	4
5a	6.68 - 8.10, m	16H	Pyridyl + Phenyl
5b	6.75 - 8.25, m	15H	Pyridyl + Phenyl
5c	6.70 - 8.20, m	15H	Pyridyl + Phenyl
5d	2.35, s	3H	CH ₃
	6.75 - 7.70, m	15H	Pyridyl + Phenyl
5e	3.78, s	3H	-OCH ₃
	6.55 - 8.10, m	15H	Pyridyl + Phenyl
5f	5.95, s	2H	O ₂ CH ₂ -
	6.40 - 8.00, m	14H	Pyridyl + Phenyl
5g	3.70 - 3.75, m d(J = 5 Hz.)	6H	di - OCH ₃
	6.58 - 8.35, m	14H	Pyridyl + Phenyl
5h	6.58 - 8.15, m	15H	Pyridyl + Phenyl
5i	2.40, s	3H	-CH ₃
	6.60 - 7.90, m	14H	Pyridyl + Phenyl
5j	3.80, s	3H	-OCH ₃
	6.65 - 8.00, m	14H	Pyridyl + Phenyl
5k	6.85 - 8.25, m	14H	Pyridyl + Phenyl
5l	6.30 - 8.22, m	14H	Pyridyl + Phenyl

s = singlet, d = doublet, m = multiplet

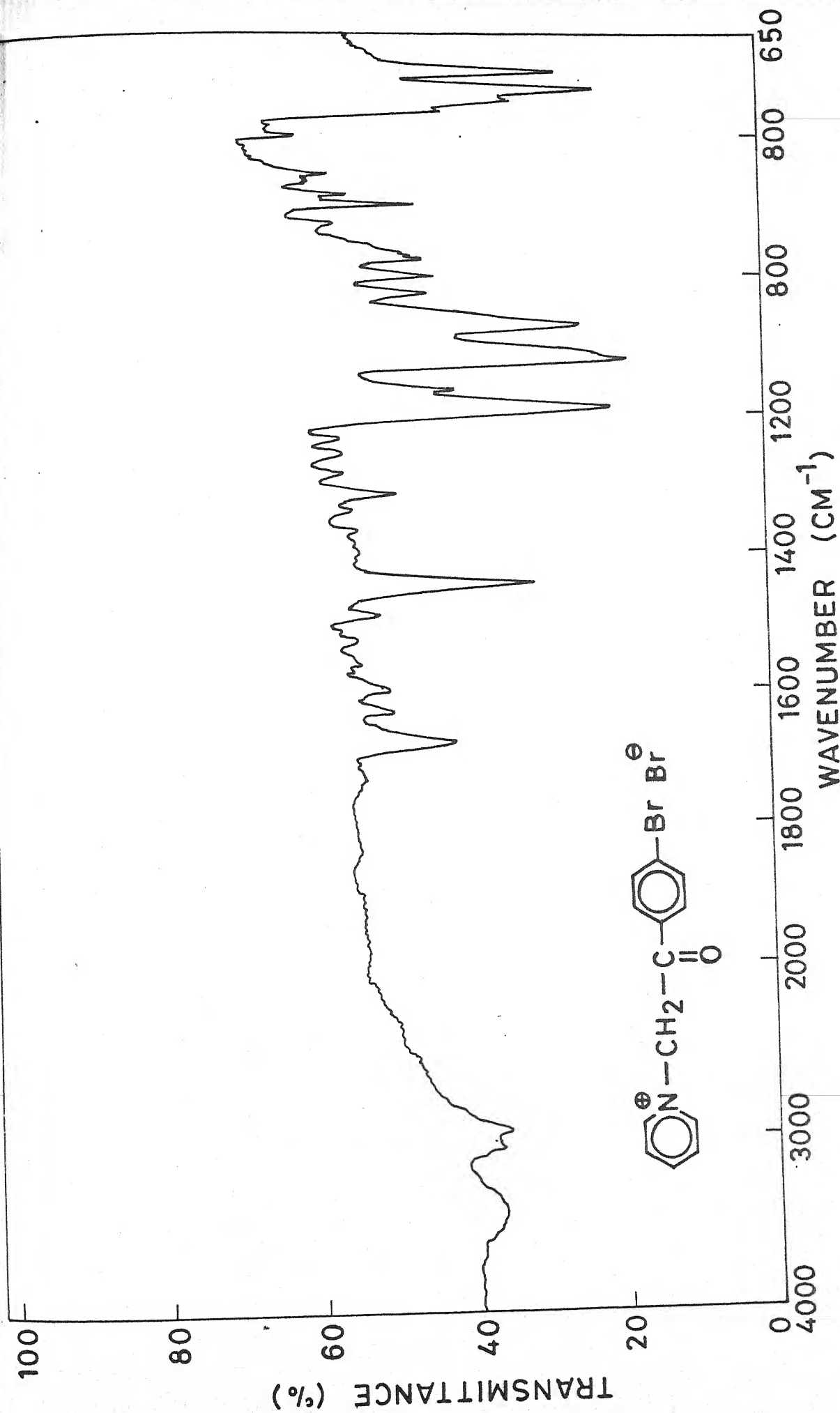


FIG. II-1 IR SPECTRUM OF SALT (1a)

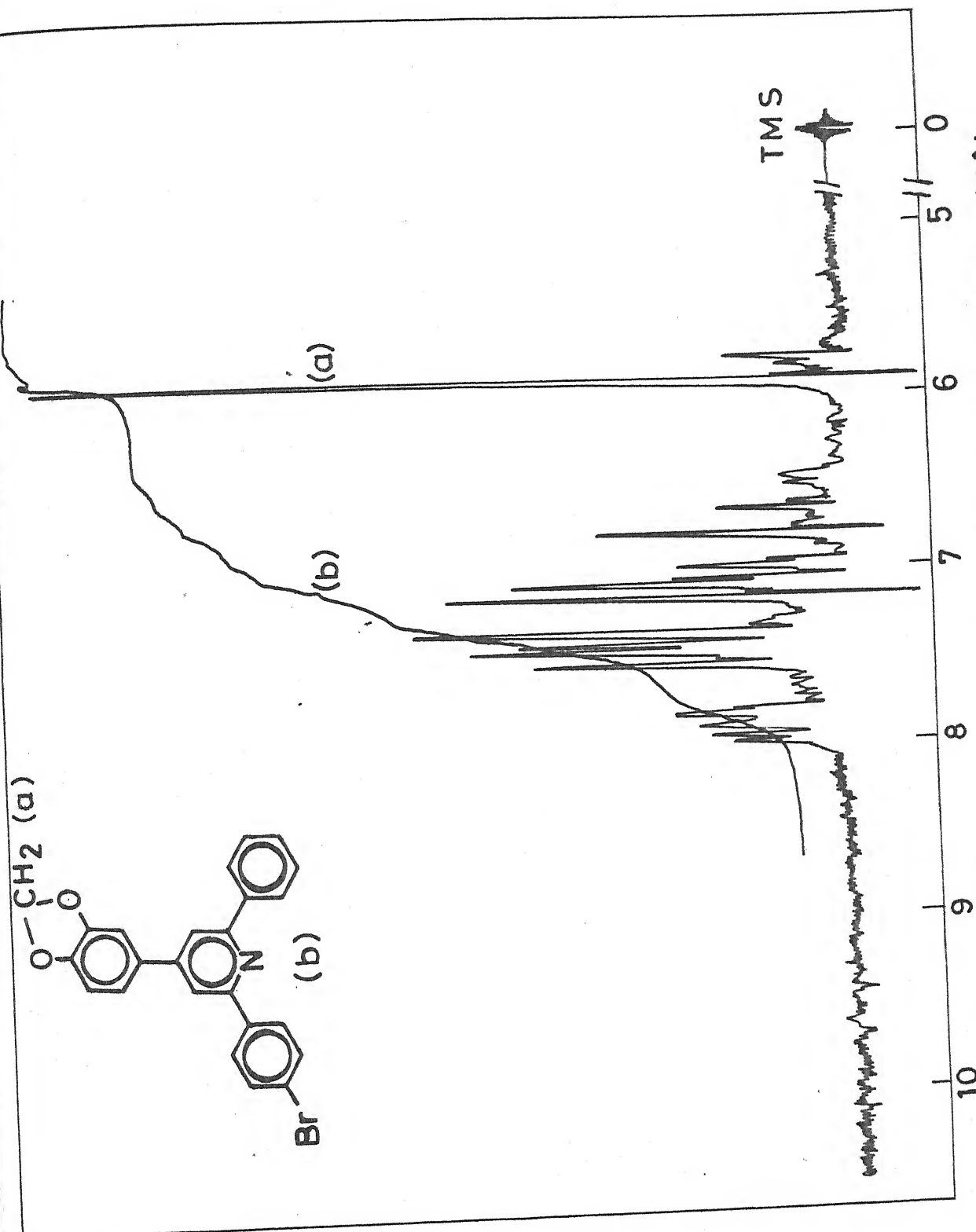


FIG.11.2 NMR SPECTRUM OF COMPOUND (5f)

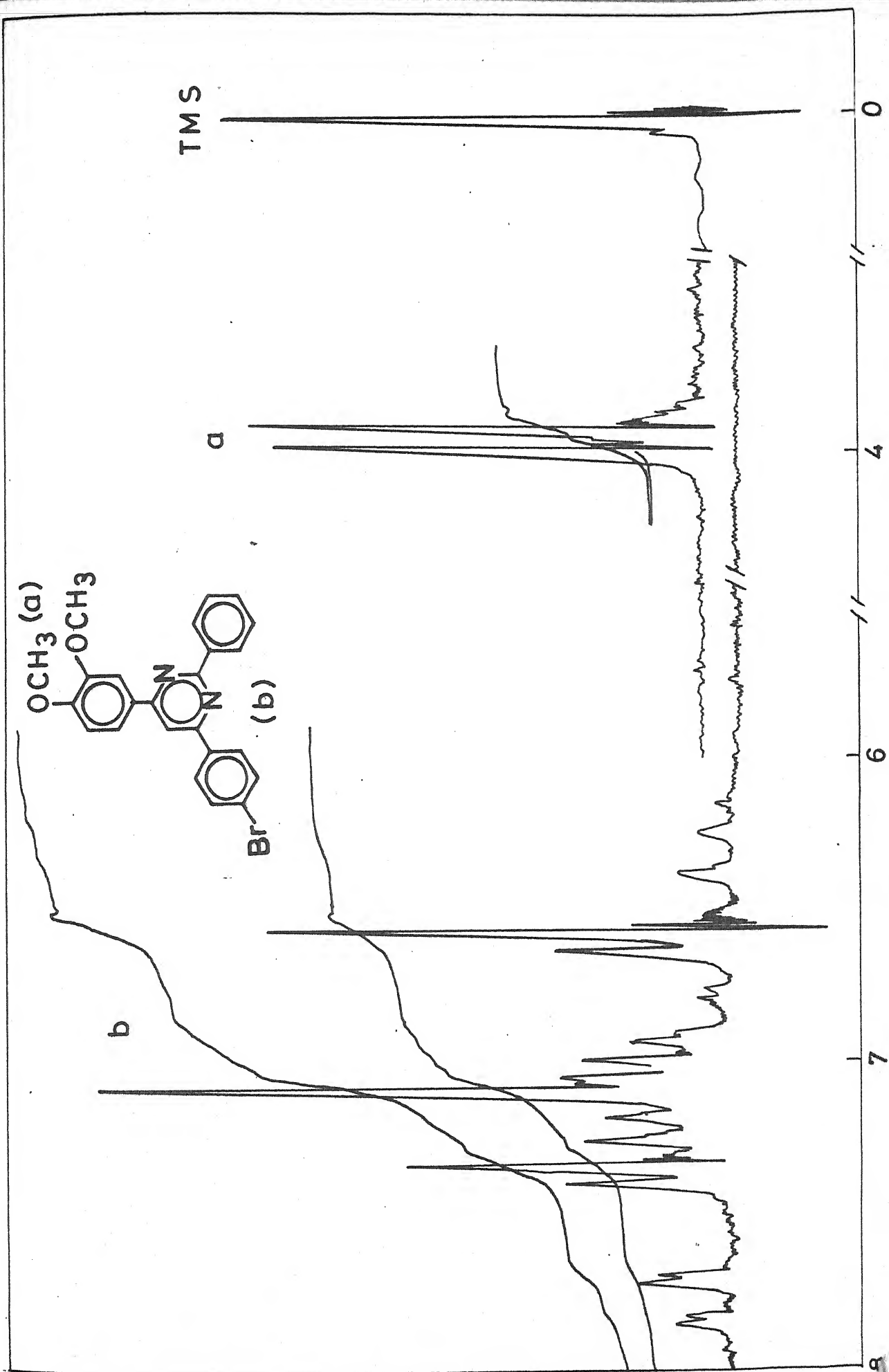


FIG. II-3 NMR SPECTRUM OF COMPOUND (5g)

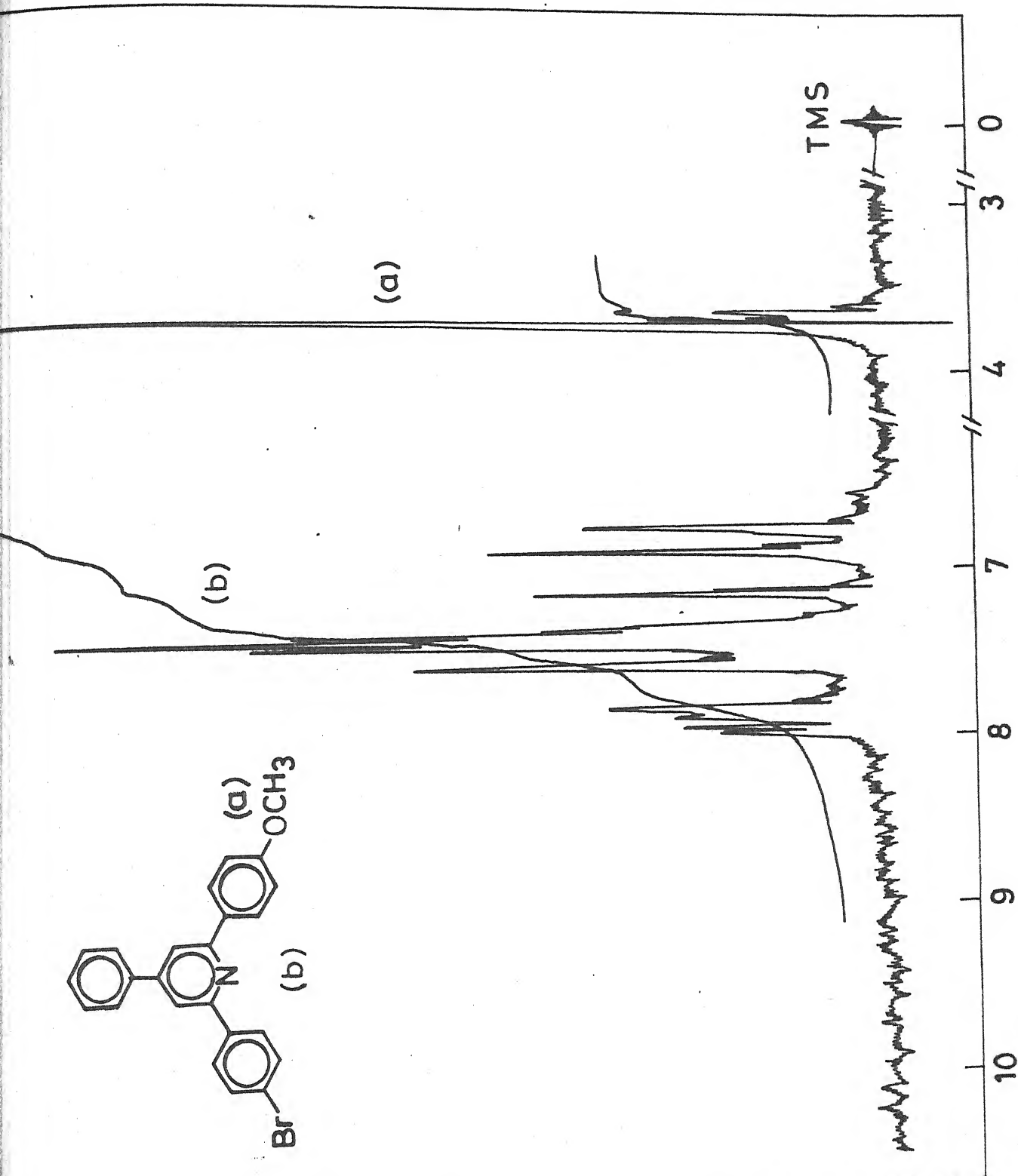
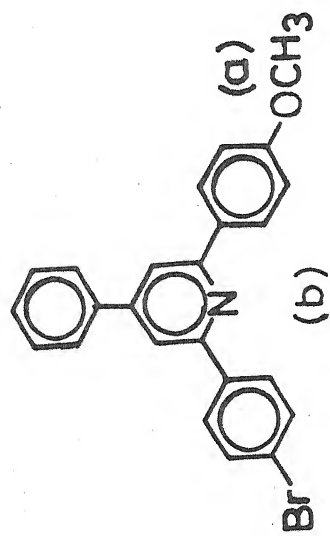


FIG. II-4 NMR SPECTRUM OF COMPOUND (5k)

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CHAPTER - III

REACTIONS OF NON-STABLE CYCLOIMMONIUM, PHOSPHONIUM AND
SULFONIUM YLIDES WITH α, β - UNSATURATED CARBONYL
COMPOUNDS : SYNTHESSES OF SOME NEW 1, 3 - DIARYL - 5-
NITRONAPHTHALENES

REACTIONS OF NON-STABLE CYLOIMMONIUM, PHOSPHONIUM AND
SULFONIUM YLIDES WITH α, β - UNSATURATED CARBONYL
COMPOUNDS : SYNTHESIS OF SOME NEW 1, 3 - DIARYL - 5 -
NITRONAPHTHALENES

3.1. ABSTRACT :

O - nitrobenzylpyridinium bromide, O - nitrobenzyltriphenylphosphonium bromide and O - nitrobenzyltrimethylsulfonium bromide have been prepared by the alkylation of pyridine, triphenylphosphine and trimethylsulfide with O - nitrobenzylbromide in acetone at the reflux temperature. The reaction of these salts with a wide variety of α, β - unsaturated carbonyl compounds in presence of sodium acetate and acetic acid with anhydrous ZnCl_2 at the reflux temperature gave 1,3-diaryl - 5 - nitronaphthalenes in 45 - 75% yields. Anhydrous ZnCl_2 is used as a cyclisation as well as dehydrating agent. Anhydrous AlCl_3 can also be used in place of anhydrous ZnCl_2 to afford the same naphthalene derivatives. The structures of the naphthalene derivatives were established with the help of elemental analysis and IR and NMR spectral data. It appears that the reaction takes place via the nucleophilic attack of ylide carbanion on the β - carbon of the α, β - unsaturated ketone to form an intermediate betaine which undergoes cyclization in presence of anhydrous ZnCl_2 or AlCl_3 to form naphthalene

derivatives.

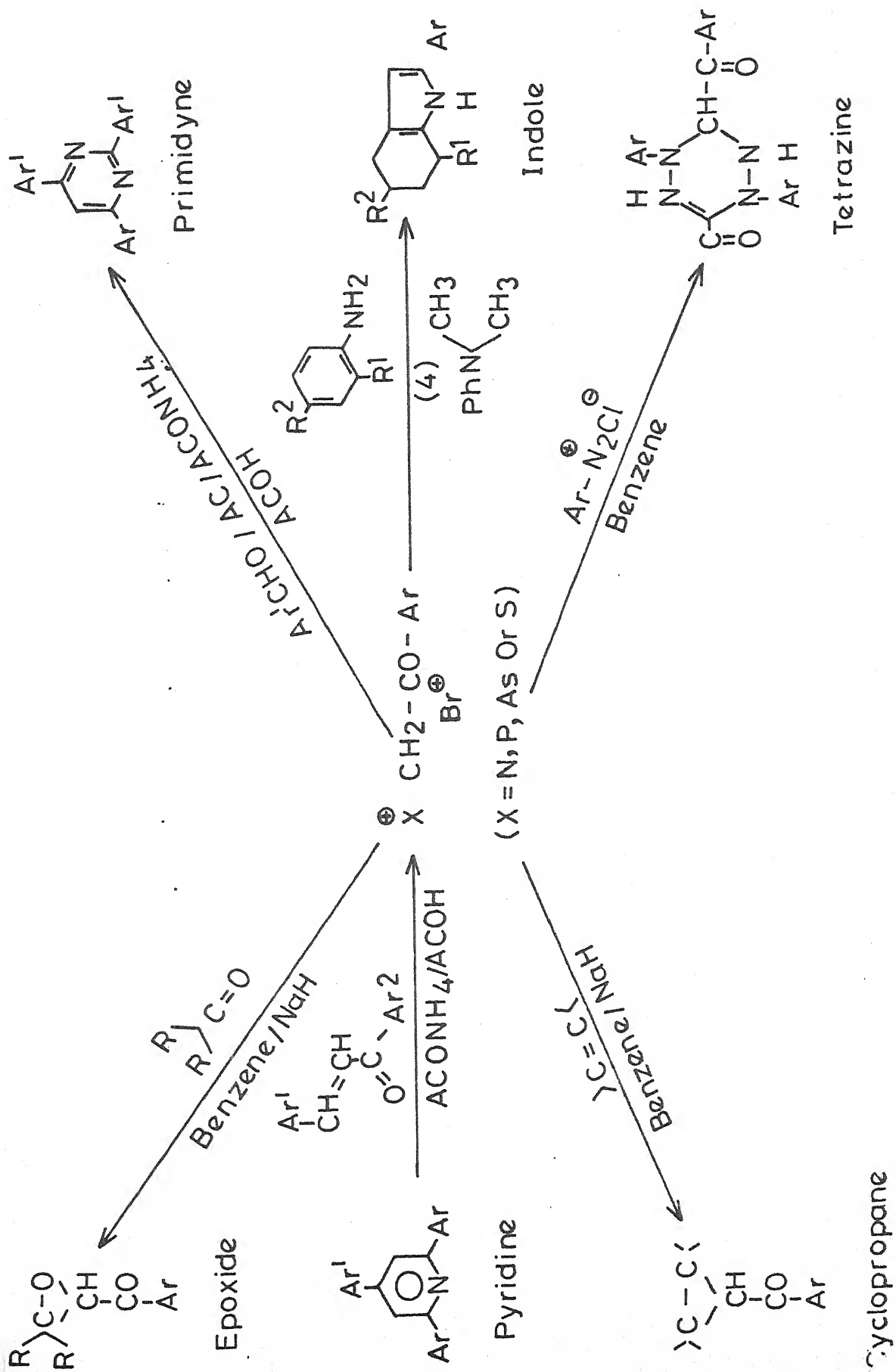
An attempt has been made to establish the relative stability of the cycloimmonium, phosphonium ylides and π -sulfuranes on the basis of yields of the nitronaphthalenes obtained by using the three types of ylides.

3.2. INTRODUCTION :

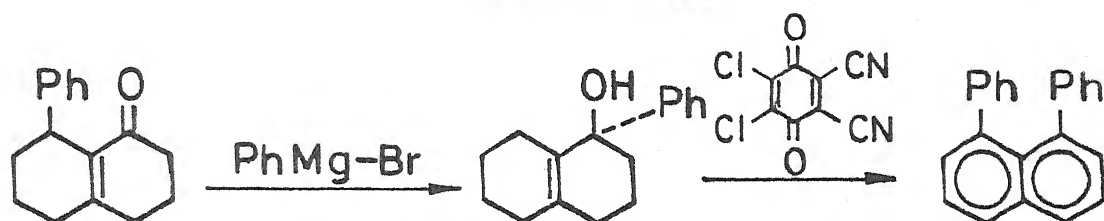
A survey of literature reveals that sulfonium salts and ylides have been utilized in the synthesis of a large variety of cyclic and heterocyclic compounds.¹ Noteworthy in this regard are the syntheses of cyclopropanes,^{2,3} epoxides,⁴ pyridines,⁵ pyrimidines,⁶ indoles⁷ and tetrazines.⁸ In many reactions, the route was found analogous to that of pyridinium, phosphonium and arsonium ylides (Scheme III.1). Thus, sulfonium salts, when coupled with α, β -unsaturated ketones in presence of ammonium acetate in acetic acid gave 2,4,6 - triarylpyridines analogous to the corresponding pyridinium and phosphonium salts as reported in chapter II. Sulfonium salts, on reaction with diazonium salts, also afforded tetrazines, the reaction is analogous to that of corresponding pyridinium and phosphonium salts.

Recently, naphthalene derivatives have been synthesised by the interaction of pyridinium⁹ and arsonium salts with α, β -unsaturated ketones in presence of anhydrous ZnCl_2 (Scheme III.2-3). But the course of reaction

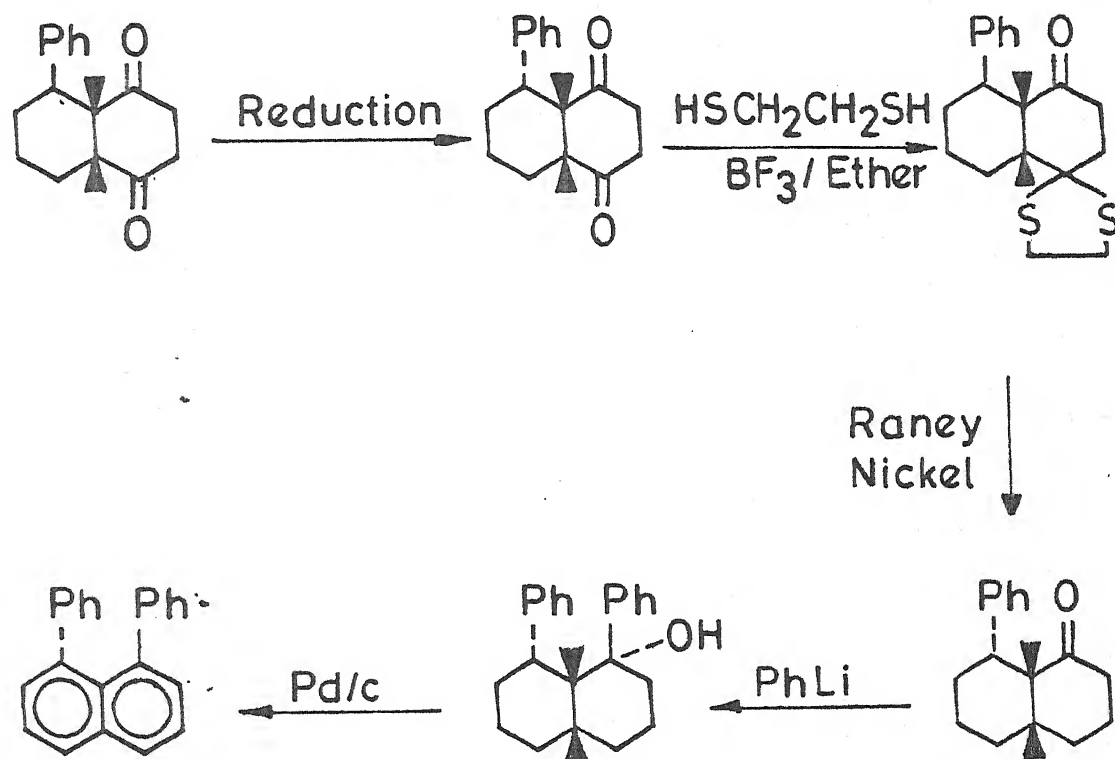
Scheme III-1



Scheme III.2



Scheme III.3



with sulfonium and phosphonium salts leading to the syntheses of naphthalene derivatives has not been explored so far.

In the present chapter we have reported the results of investigations on reactions of O-nitrobenzylpyridinium bromide, O-nitrobenzyltriphenylphosphonium bromide and O-nitrobenzyltrimethylsulfonium bromide and their ylides with a variety of α, β - unsaturated ketones in presence of anhydrous ZnCl_2 . The investigations were carried out to gain an insight into the comparative behaviour of these ylides and also to further explore the applicability in the field.

3.3. RESULTS AND DISCUSSION :

The reaction of pyridines with O-nitrobenzyl bromide in acetone at reflux temperature gave O-nitrobenzylpyridinium bromide (1) in about 60% yield. Its structure was established by elemental and spectral data. The IR spectrum showed a characteristic absorption band of strong intensity at 3060 cm^{-1} due to C - H stretching vibration of methylene group attached to a position adjacent to nitrogen atom. Characteristic absorption bands due to $-\text{NO}_2$ group in salt (1) were exhibited at 1515 and 1300 cm^{-1} . The NMR spectrum of the salt showed a strong singlet at $\delta 6.30$ due to methylene protons.

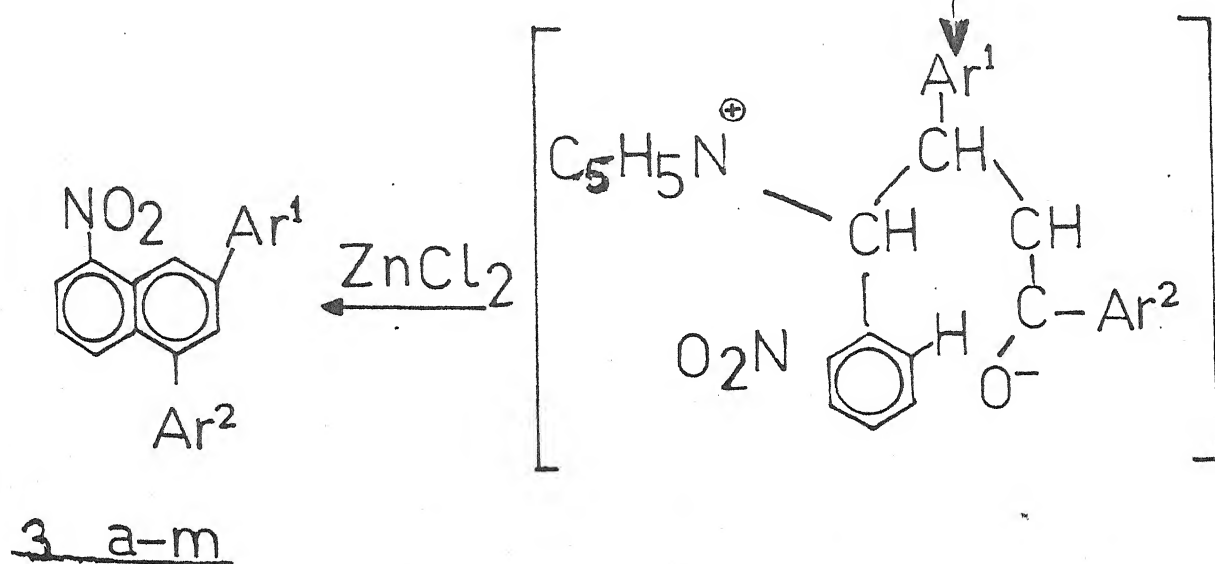
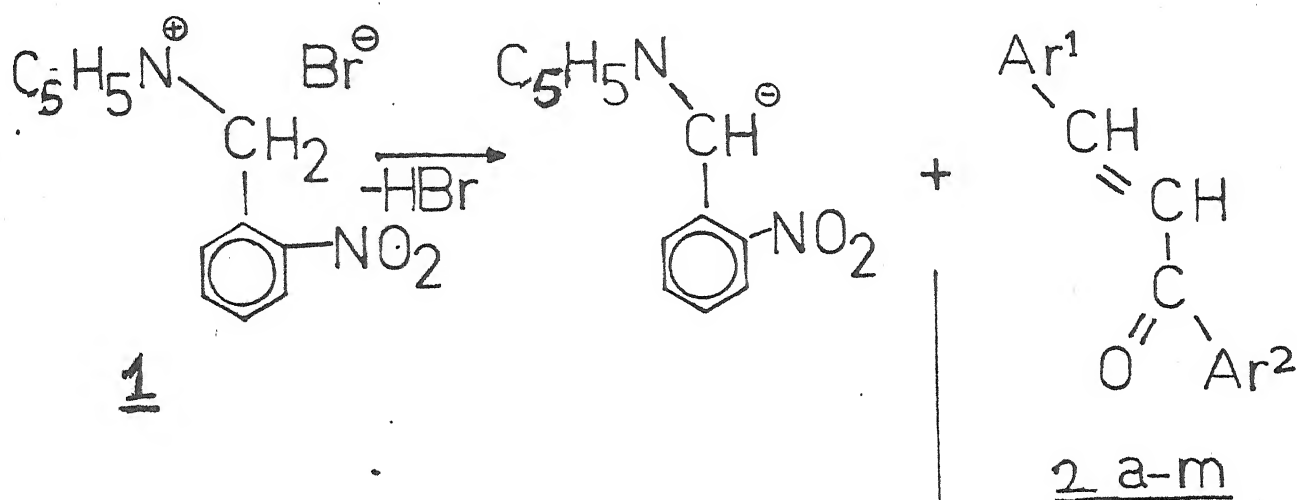
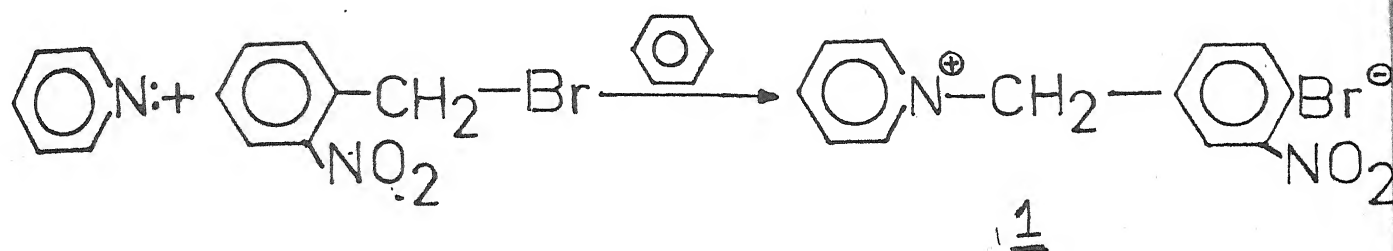
Aromatic protons appeared in the range δ 6.80 - 8.40.

The reaction of salt(1) with α, β -unsaturated ketones (2a-m) in a mixture of sodium acetate and glacial acetic acid using anhydrous ZnCl_2 was carried out at the reflux temperature to give 1,3-diaryl-5-nitronaphthalenes (3a-m) (Scheme III.4) (Route A).

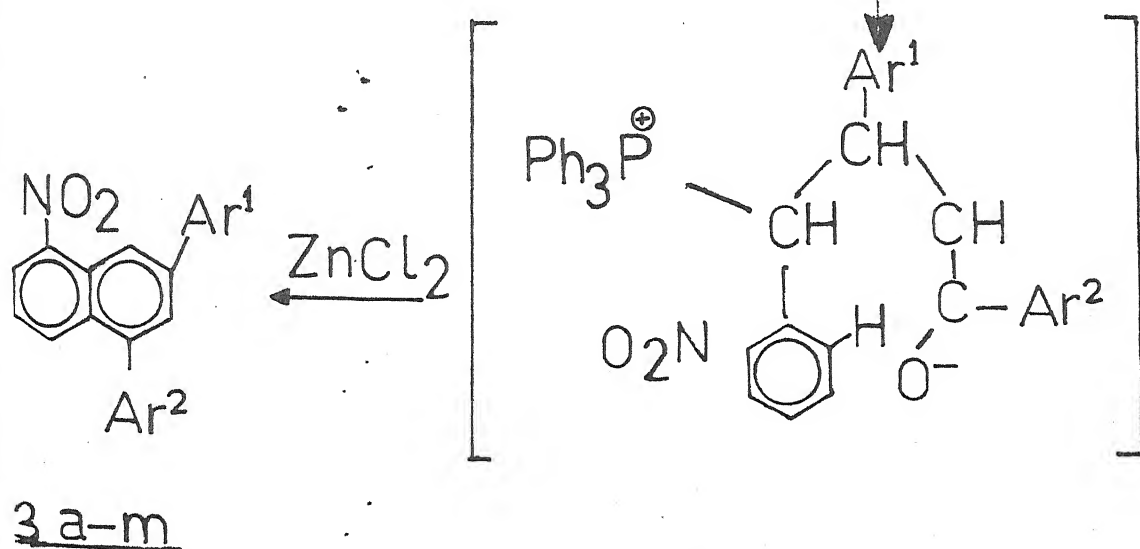
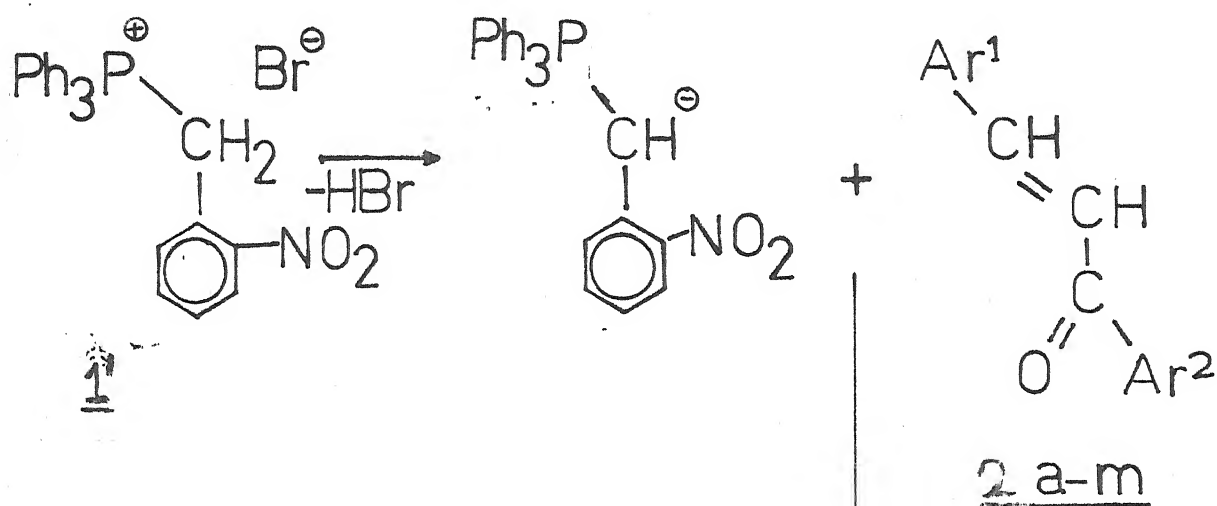
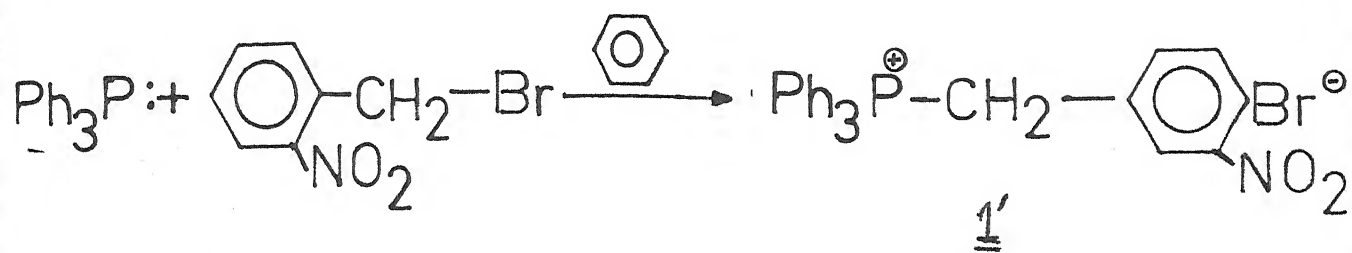
The reaction of triphenylphosphine with O-nitrobenzyl bromide in acetone at reflux temperature gave O-nitrobenzyltriphenylphosphonium bromide (1') in about 60% yield. The structure of the salt (1') was established with the help of elemental and spectral data. The IR spectrum of salt (1') showed a characteristic absorption band of strong intensity at 3070 cm^{-1} due to C-H stretching vibrations of the methylene group attached to a position adjacent to P atom. Characteristic absorption bands due to $-\text{NO}_2$ group were observed between 1510 and 1315 cm^{-1} . The NMR spectrum of the salt (1') showed a strong singlet at δ 6.60 due to methylene protons. The aromatic protons were exhibited in the range δ 7.05 - 8.30.

The reaction of the salt (1') with α, β -unsaturated ketones (2a-m) in a mixture of sodium acetate and acetic acid and in presence of ZnCl_2 was carried out at reflux temperature to yield 1,3-diaryl-5-nitronaphthalenes (3a-m) in 40 to 64% yields (Scheme III.5)

Scheme III.4



Scheme III.5



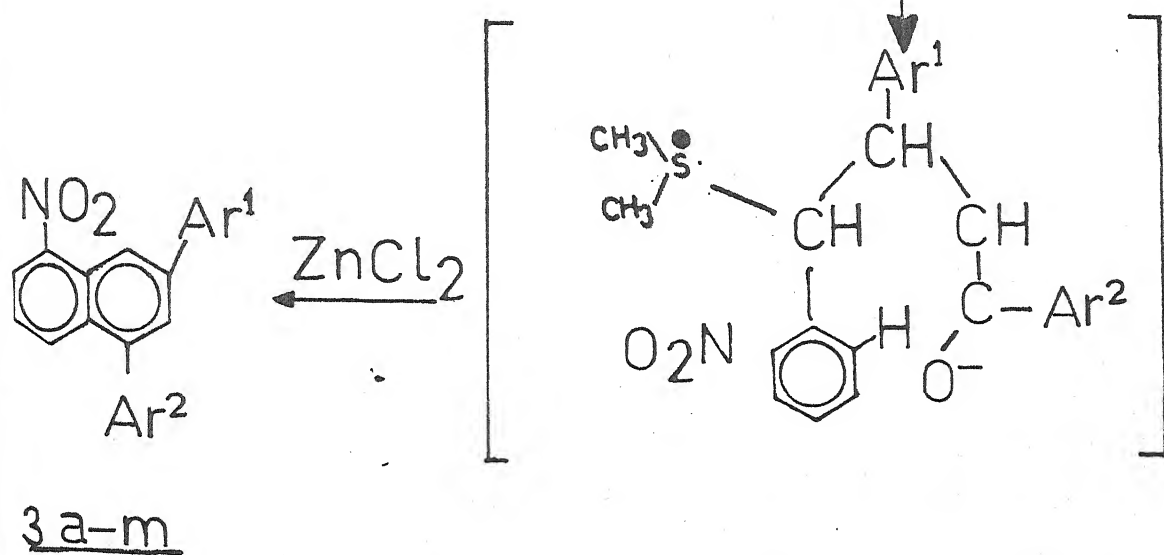
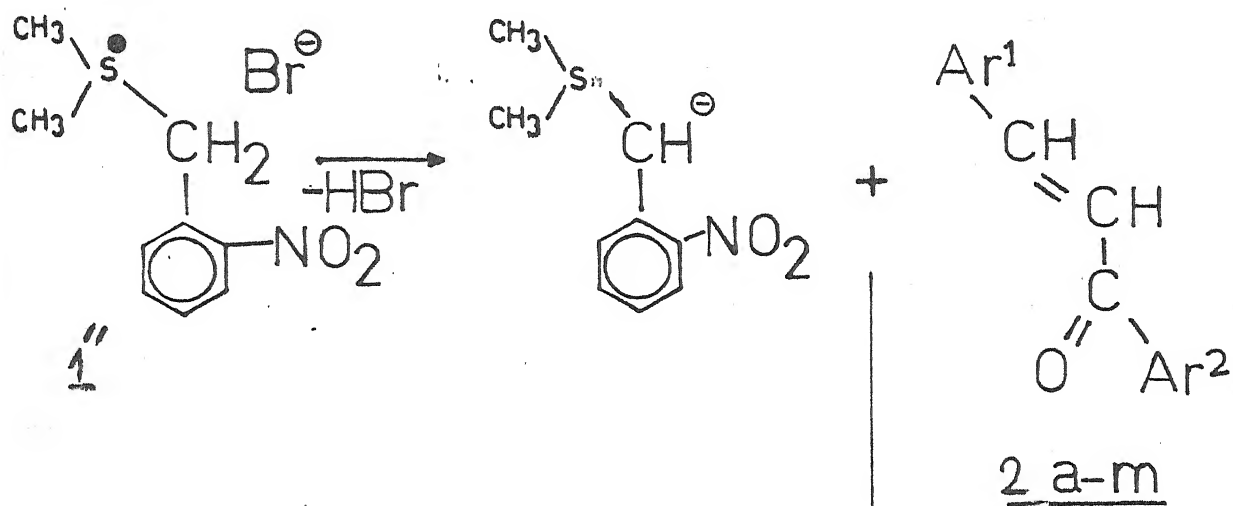
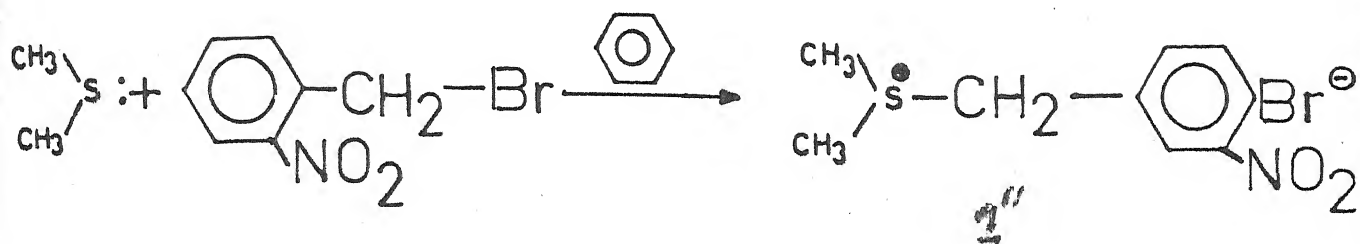
(Route B).

The reaction of dimethylsulfide with *O* - nitrobenzyl bromide in acetone at reflux temperature gave *O* - nitrobenzyl dimethylsulfonium bromide (1ⁿ) in about 65% yield. The structure of this salt was characterised by elemental and IR and NMR spectral data. The IR spectrum of the salt (1ⁿ) showed a characteristic absorption band of strong intensity at 3040 cm^{-1} due to C - H stretching vibrations of the methylene group attached at a position adjacent to sulfur atom. Characteristic absorption bands due to $-\text{NO}_2$ group in the salt were visible at 1510 and 1300 cm^{-1} . The NMR spectra of the salt (1ⁿ) showed an intense singlet at δ 5.20 due to methylene protons. A sharp singlet at δ 3.05 was due to two methyl groups directly attached to the sulfonium group. δ 7.0 - 8.30 was the range in which the aromatic protons were indicated.

The reaction of the salt (1ⁿ) with a series of α, β - unsaturated ketones (2a-m) in a mixture of sodium acetate and glacial acetic acid using anhydrous ZnCl_2 was carried out at reflux temperature to form 1,3 - diaryl - 5 - nitronaphthalenes (3a-m) in 45-76% yields (Scheme III.6) (Route C).

In each of the three reactions reported above, identical 1-3-diaryl-5- nitronaphthalenes (3a-m) were

Scheme III.6



produced by the reaction of a wide variety of α, β -unsaturated ketones separately with O-nitrobenzylpyridinium bromide, O-nitrobenzyltriphenylphosphonium bromide and O-nitrobenzyltrimethylsulfonium bromide. In each case the yields of the naphthalene derivatives (3a-m) are dependent upon the nature of substituents attached to the chalcone moieties (2a-m) as well as on the electron attracting behaviour of the $-\text{NO}_2$ group of the salt (1, 1', or 1'').

In all the three routes, the reaction seems to proceed via the nucleophilic attack of the ylide carbanion formed ^{by} the dehydrohalogenation of the salt (1, 1' or 1'') on the β -carbon of the α, β -unsaturated ketone (2a-m) to form an intermediate betaine which then undergoes cyclization in presence of ZnCl_2 to form the naphthalene derivatives.

All the naphthalenes (3a-m) obtained during the present investigations are crystalline solids generally soluble in chloroform, pyridine and acetone. All the physical and spectral data are included in tables III.1 to III.3. All the compounds are new and give satisfactory elemental analysis. The IR spectral data of the naphthalenes (3a-m) show a double absorption maxima in the region $1620-1600 \text{ cm}^{-1}$ which are assigned to the $\text{C}=\text{C}$ double bond. The strong bands in the region $900-865 \text{ cm}^{-1}$ were characteristic of absorption of the naphthalene ring. The nitro group of

the naphthalene derivatives showed a diagnostic strong asymmetrical stretching band around $1350-330\text{ cm}^{-1}$. The NMR spectral data of the compounds, in general, showed aromatic multiplet in the range δ 6.40 - 8.30. The methyl and the methoxy groups were absorbed in the range δ 4.40 - 2.55 and δ 3.70 - 3.85 respectively.

The extent of yields of the naphthalene derivatives via the three routes may be utilised to make some empirical generalisations as to the comparative reactivity and stability of the cycloimmonium (pyridinium), phosphonium and sulfonium ylides. It was observed (table III.1) that almost invariably the route A gave maximum yield followed by route C. Route B gave the minimum yields of the naphthalene derivatives. It was thus possible to characterise the order of reactivity as cycloimmonium ylides $>$ π -sulfuranes $>$ phosphonium ylides.

The above order of reactivity yielded by experimental results may also be justified on the basis of theoretical considerations.

The greater reactivity of pyridinium ylides as compared to phosphonium and sulfonium ylides may be understood in the context of former's greater nucleophilicity due to total lack of $d\pi - p\pi$ bonding. In the case of π -sulfuranes and phosphonium ylides, $d\pi - p\pi$ bonding may

occur to a considerable extent to favour the ylene form. This results in lesser ylidic character and hence lesser yields of the naphthalene derivatives.

Comparison between reactivity of phosphonium ylides and π - sulfuranes is also possible although both are characterised by $d\pi - p\pi$ bonding. The greater reactivity of π -sulfuranes may probably be attributed to the presence of two methyl groups which makes them more nucleophilic compared to phosphonium ylides containing three phenyl groups. Three phenyl groups offer greater resonance stabilisation and also greater steric hinderance. Obviously, therefore, π - sulfuranes are more reactive of the two.

3.4. EXPERIMENTAL :

3.4.1. STARTING MATERIALS :

All the reagents were obtained from commercial sources i.e. BDH, S. Merck, E. Merck, SISCO etc. The starting materials were prepared as per the reference cited: Thus, O - nitrobenzyl bromide was prepared by the direct bromination of O - nitrotoluene at reflux temperature. The substituted benzyldine acetophenones and benzyldine acetophthalenes were prepared by stirring the equimolar amounts of aromatic aldehyde and acetophenone in ethanolic solution containing 2% NaOH at 0°C . The resulting

precipitate of α, β -unsaturated ketones was recrystallised from ethanol.¹²

I. Preparation of O-nitrobenzylpyridinium bromide(1) :

A mixture containing 100 m mole of O-nitrobenzylbromide and 100 m mole of pyridine in 100 ml of benzene or acetone was refluxed on a water bath for 6-8 hours. Excess of the solvent was evaporated and petroleum ether (60-80°) was added to precipitate O-nitrobenzylpyridinium bromide(1). The salt was twice recrystallised from CHCl_3 : n-hexane (1:2) to give a yellowish crystalline solid m.p. 180-82°C. Yield 80%.

Analytical data found % C 48.50 H 3.70

Calcd % C 48.81 H 3.72

IR(KBr) data (cm^{-1}) : 3060 (N-CH_2), 1515 and 1300 (NO_2)

NMR (CDCl_3) data δ (ppm) 6.30 (s, 2H, CH_2) 6.80-8.40(m, 9H, Ar-H)

II. Preparation of O-nitrobenzyltriphenylphosphonium bromide (1'):

A mixture of 100m mole of O-nitrobenzylbromide and 100m mole of triphenylphosphine in 100 ml of anhydrous benzene or acetone was refluxed on a water bath for 6-8 hours. The excess of the solvent was evaporated and petroleum ether (60-80°) was added to precipitate O-nitrobenzyltriphenylphosphonium bromide (1'). The salt was recrystallised twice from CHCl_3 : n-hexane (1:2) to give

a white crystalline solid. m.p. 247-49°C. Yield 65%.

Analytical data found % C 67.20 H 4.61

Calcd % C 67.11 H 4.70

IR (KBr) data (cm^{-1}) 3070 (ν p- CH_2)

1510 and 1315 (ν NO_2)

NMR (CDCl_3) data δ (ppm)

5.75 (d, 15 Hz, 2H, CH_2)

7.05-8.30 (m, 19H, ArH)

III. Preparation of O-nitrobenzyldimethylsulfonium bromide(1ⁿ)

A mixture consisting of 100 m mole of O-nitrobenzylbromide and 100 m mole of dimethylsulfide in 100 ml of anhydrous benzene or acetone was refluxed on a water bath for 6-8 hours. Excess of the solvent was evaporated and petroleum ether (60-80°C) was added to precipitate O-nitrobenzyldimethylsulfonium bromide (1ⁿ). The salt was recrystallised twice from CHCl_3 : n-hexane (1:2) to get a yellow crystalline solid. m.p. 142°C-144°C. Yield 75%.

Analytical data found % C 38.89 H 4.29

Calcd % C 38.84 H 4.31

IR (KBr) data cm^{-1} : 3040 (ν C-H) of CH_2 -S

1510 and 1300 (ν NO_2)

NMR (CDCl_3) data δ (ppm):

3.05 (s, 6H, d1 - CH_3)

5.20 (s, 2H, CH_2 - S <)

7.0-8.30 (m, 4H, ArH)

3.4.2. FINAL PRODUCTS :

1. Preparation of 1,3-diaryl-5-nitronaphthalenes(3a-m):

A solution of 3m mole of the salt (1,1' or 1''), 1 gm of anhydrous ZnCl_2 or AlCl_3 and 1 gm of sodium acetate in 20 ml of glacial acetic acid was taken in a 100 ml round bottom flask equipped with a reflux condenser and a magnetic stirrer. The mixture was stirred at the room temperature for 1-2 hours. 3m mole of the α , β -unsaturated ketone (2a-m) dissolved in 10 ml of glacial acetic acid was added dropwise to the mixture and the resulting solution was stirred at 200°C for 5-10 hours. Then the solution was allowed to stand overnight at the room temperature. This was followed by the addition of 25 ml of ice cold water to the solution. The precipitate so obtained was filtered off, dried and chromatographed over neutral alumina. Elution with benzene : petroleum ether (1:1) gave fine crystalline solid crystals of the titled compound as shown in table III.1.

TABLE III.1

PHYSICAL PROPERTIES OF 1,3 - DIARYL - 5 - NITRONAPHTHALENES (3a-m)

Comp- ound	Ar ¹	Ar ²	Route	m.p. °C	Yield %	C	H	N
1	2	3	4	5	6	7	8	9
3a	C ₆ H ₅	C ₆ H ₅	A	96-98	70	81.25	4.65	4.36
			B	97-98	65	81.30	4.70	4.30
			C	95-98	68	81.20 (81.20)	4.68 (4.61)	4.32 (4.30)
3b	C ₆ H ₅	4-CH ₃ C ₆ H ₄	A	166-68	76	81.92	5.05	4.16
			B	165-67	64	81.84	5.12	4.08
			C	169-69	72	81.82 (81.89)	5.08 (5.01)	4.10 (4.12)
3c	C ₆ H ₅	4-CHOC ₆ H ₄	A	124-126	72	77.60	4.72	3.16
			B	125-126	60	77.68	4.76	3.12
			C	125-127	65	77.62 (77.74)	4.68 (4.78)	3.14 (3.10)

1	2	3	4	5	6	7	8	9
3d	C_6H_5	4-Cl C_6H_5	A	134-36	68	73.95	3.82	3.68
			B	133-36	55	73.90	3.86	3.64
			C	134-35	64	73.94 (73.99)	3.84 (3.89)	3.62 (3.61)
3e	C_6H_5	3,4- C_2H_2 C_6H_3	A	135-137	70	74.71	4.02	3.78
			B	136-138	60	74.78	4.09	3.82
			C	134-137	65	74.70 (74.80)	4.03 (4.06)	3.85 (3.79)
3f	4- CH_3 C_6H_4	C_6H_5	A	158-160	60	81.92	5.09	4.18
			B	158-160	45	81.96	5.12	4.14
			C	159-162	55	81.90 (81.89)	5.10 (5.01)	4.10 (4.12)
3g	4- CH_3 C_6H_4	4- CH_3 C_6H_4	A	108-110	65	78.16	5.18	3.70
			B	109-112	57	78.20	5.14	3.74
			C	109-111	60	78.21 (78.10)	5.16 (5.14)	3.75 (3.79)

1/110/1

1	2	3	4	5	6	7	8	9
3h	4-Cl C ₆ H ₄	4-NO ₂ C ₆ H ₄	A	136-138	60	66.15	3.20	7.07
			B	135-136	50	66.08	3.24	7.04
			C	134-136	56	66.12 (66.01)	3.18 (3.25)	7.02 (7.00)
3i	2-C ₁₀ H ₇	C ₆ H ₅	A	178-180	65	83.08	4.48	3.66
			B	179-180	55	83.12	4.47	3.69
			C	178-180	62	83.17 (83.20)	4.45 (4.55)	3.65 (3.73)
3j	2-C ₁₀ H ₇	4-Cl C ₆ H ₄	A	168-170	70	76.10	3.98	3.48
			B	168-170	55	76.12	3.99	3.50
			C	168-171	60	76.15 (76.19)	3.95 (3.90)	3.46 (3.41)
3k	2-C ₁₀ H ₇	3-CH ₃ C ₆ H ₄	A	196-198	55	82.61	5.25	3.75
			B	195-198	40	82.58	5.24	3.73
			C	196-199	50	82.53 (82.53)	5.28 (5.29)	3.76 (3.70)

1	2	3	4	5	6	7	8	9
31	4-C ₆ H ₅ .C ₆ H ₄	C ₆ H ₅	A	144-146	50	83.70	4.77	3.58
			B	143-145	40	83.76	4.74	3.51
			C	144-146	45	83.74 (83.79)	4.78 (4.73)	3.60 (3.49)
3m	2-C ₄ H ₃ S	4-CH ₃ O C ₆ H ₄	A	188-190	60	79.70	5.01	4.15
			B	188-191	45	79.76	5.04	4.18
			C	187-190	55	79.78 (79.74)	5.05 (5.00)	4.14 (4.11)

TABLE III.2

IR SPECTRAL PROPERTIES OF 1,3-DIARYL-5-NITRONAPHTHALENES (3a-m)

IR(KBr) data cm^{-1}

Compound	$\nu_{\text{C}=\text{O}}$	$\phi_{\text{C}-\text{H}}$	$\nu_{\text{C}-\text{NO}_2}$	$\nu_{\text{C}-\text{H}}$
3a	1600	995	1490, 1330	3058
3b	1605	990	1495, 1330	3060
3c	1590	992	1500, 1340	3055
3d	1610	985	1505, 1335	3080
3e	1595	990	1500, 1320	3070
3f	1610	992	1520, 1335	3060
3g	1610	995	1515, 1340	3065
3h	1615	998	1230, 1330	3060
3i	1610	995	1525, 1330	3070
3j	1615	995	1520, 1330	3070
3k	1628	990	1510, 1340	3060
3l	1630	995	1525, 1335	3065
3m	1625	990	1535, 1330	3070

ν = Stretching vibration, ϕ = out of plane deformation.

TABLE III.3

NMR SPECTRAL PROPERTIES OF 1,3-DIARYL-5-NITRONAPHTHALENES (3a-m)

Compound	H-NMR(CDCl ₃) data δ (ppm)	No. of Protons	Assignment
3a			
3b	2.45, s 6.95-8.25, m	3H 14H	CH ₃ ArH
3c	3.90, s 6.80-8.25, m	3H 14H	OCH ₃ ArH
3d			
3e	6.08, s 6.70-8.20, m	2H 13H	-CH ₂ O ₂ ⁻ ArH
3f	2.40, s 6.85-8.15, m	3H 14H	CH ₃ ArH
3g	2.30, s 3.75, s 6.80-8.25, m	3H 3H 13H	CH ₃ OCH ₃ ArH
3h	6.90-8.30, m	13H	ArH
3i	6.95-8.40, m	13H	ArH
3j	6.86-8.28, m	16H	ArH
3k	2.33, s 7.13-8.35, m	3H 16H	CH ₃ ArH
3l			
3m	3.85, s 6.80-7.95, m	3H 12H	OCH ₃ ArH

s = singlet, m = multiplet.

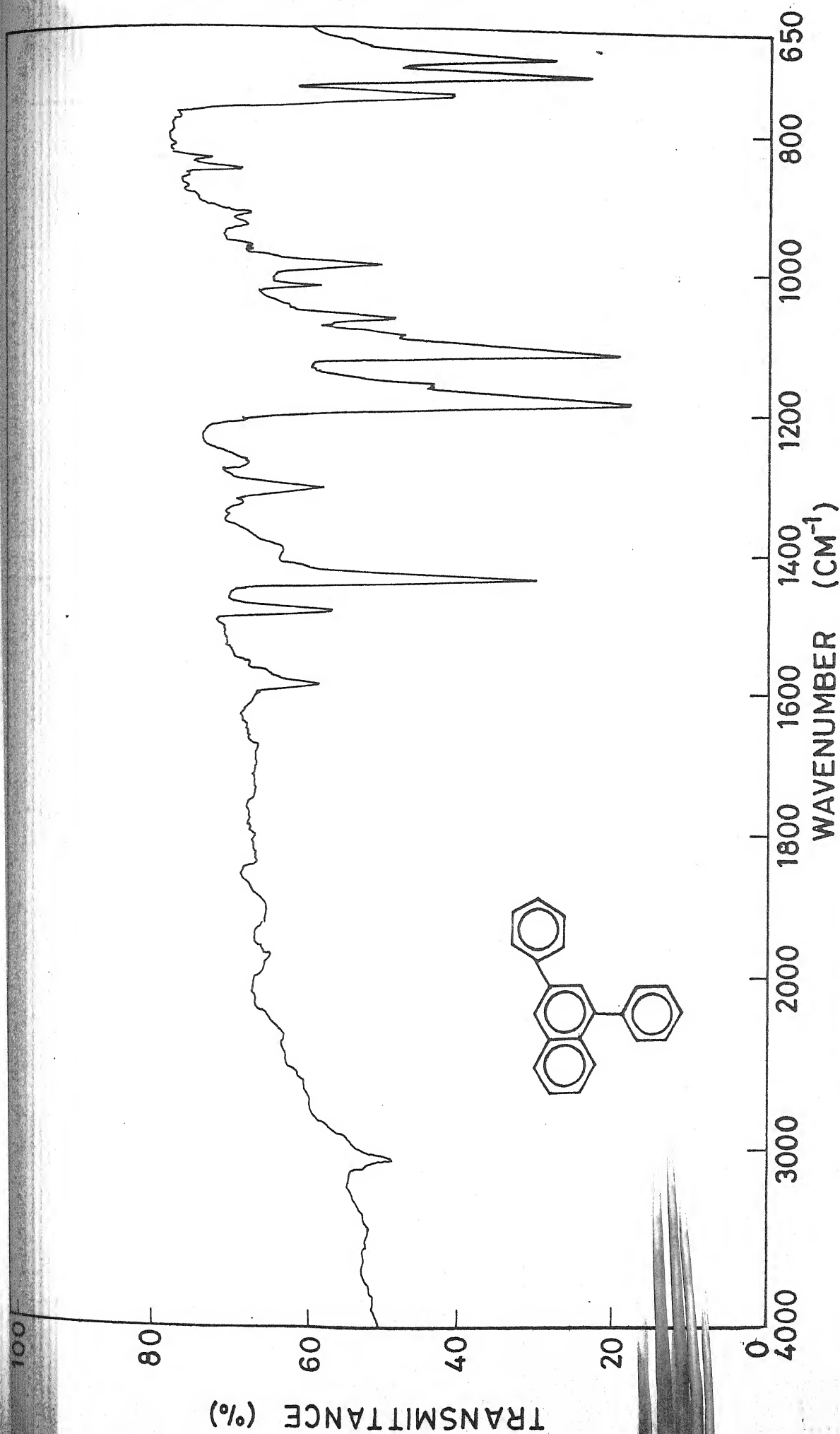


FIG. III-1 IR SPECTRUM OF COMPOUND (3a)

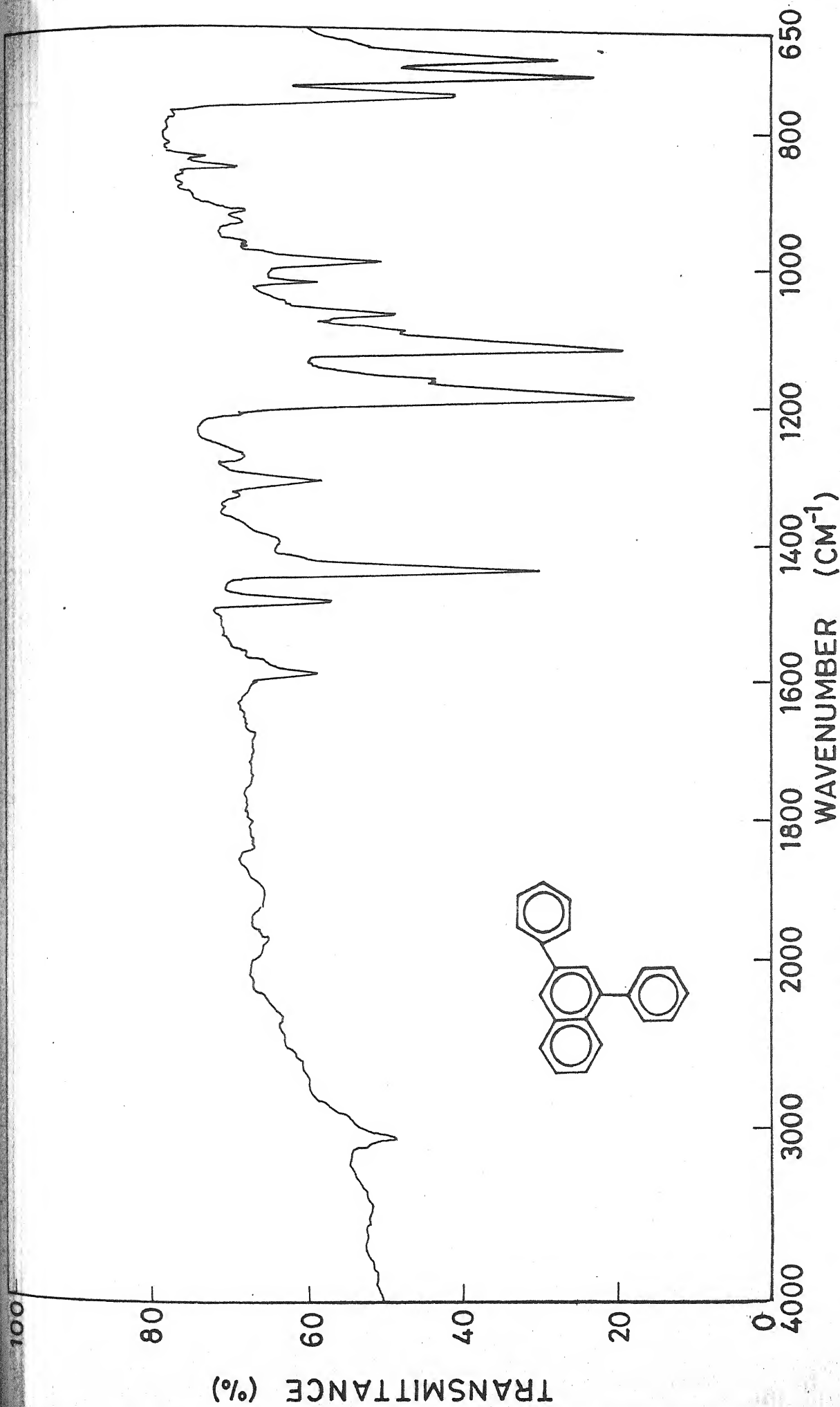
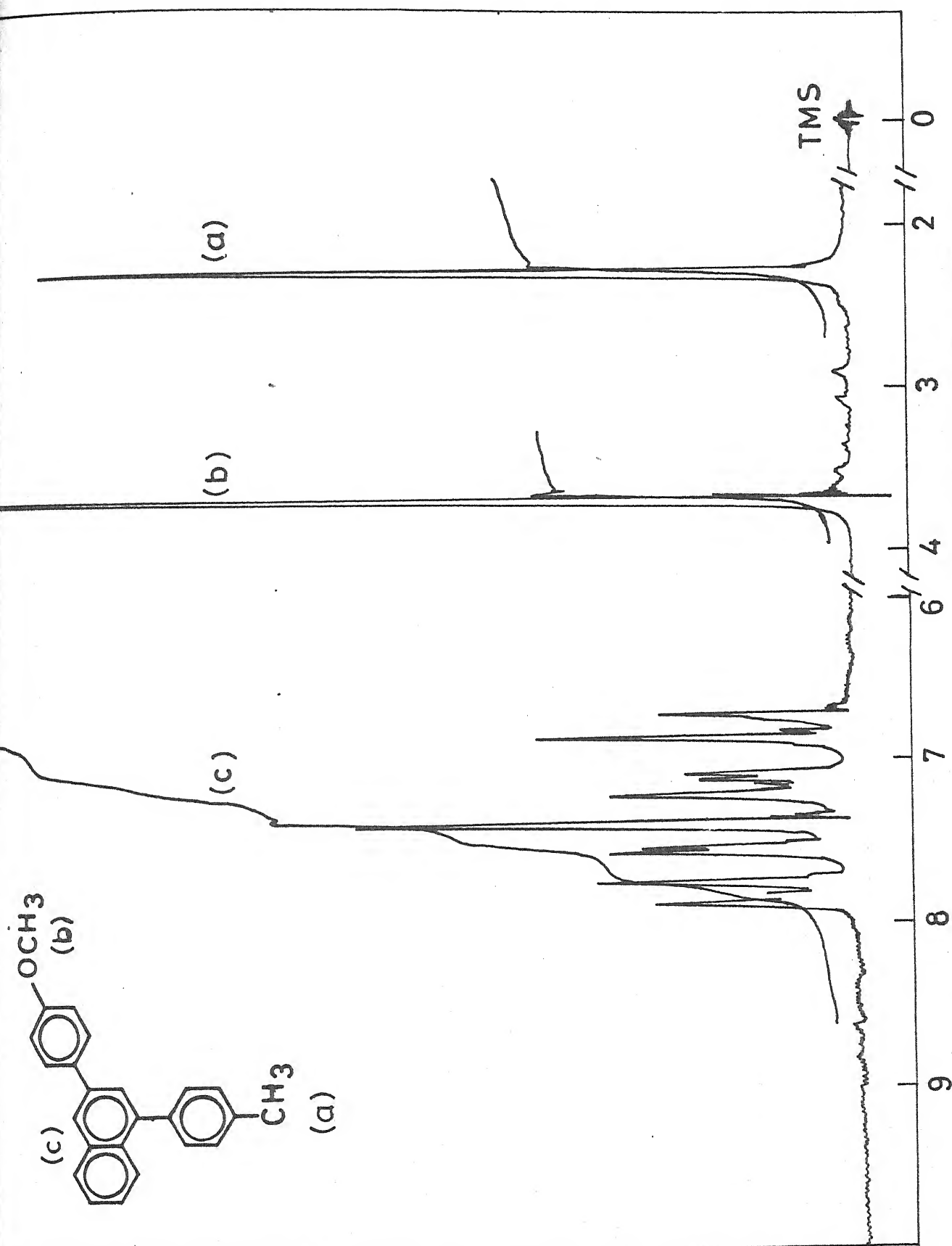


FIG. III-1 IR SPECTRUM OF COMPOUND (3a)



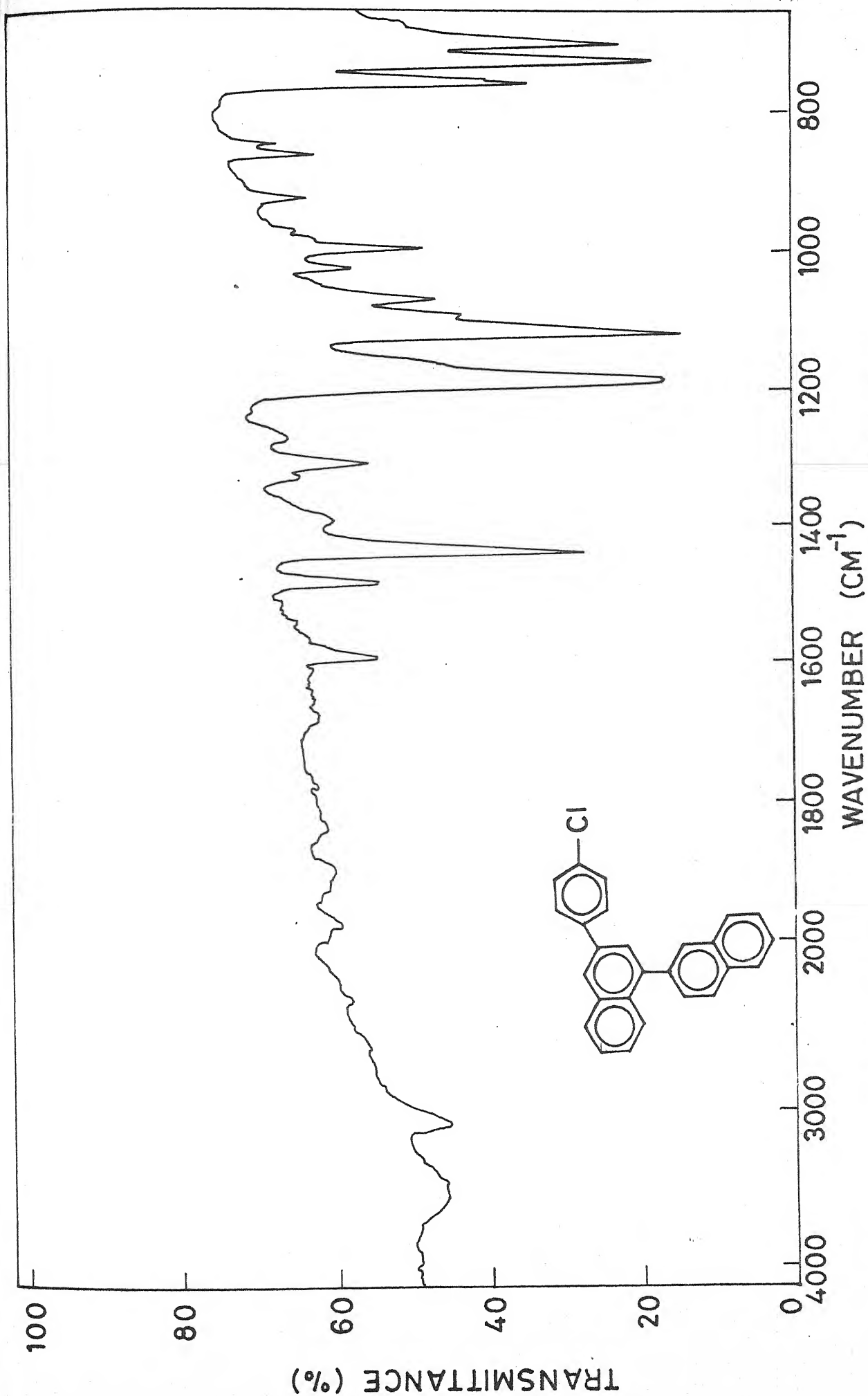


FIG. III - 3 IR SPECTRUM OF COMPOUND (3f)

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CHAPTER - IV

REACTIONS OF SUBSTITUTED PHENACYL - PYRIDINIUM,
-TRIPHENYLPHOSPHONIUM AND - DIAMETHYLSULFONIUM
BROMIDES WITH AROMATIC DIAZONIUM SALTS:SYNTHESES
OF 1, 4 - DIHYDRO - 1, 2, 4, 5 - TETRAZINES

REACTIONS OF SUBSTITUTED PHENACYL - PYRIDINIUM,
-TRIPHENYLPHOSPHONIUM AND - DIMETHYLSULFONIUM
BROMIDES WITH AROMATIC DIAZONIUM SALTS:SYNTHESES
OF 1, 4 - DIHYDRO - 1, 2, 4, 5 - TETRAZINES

4.1. ABSTRACT :

Reactions of phenacylpyridinium bromide, phenacyltriphenylphosphonium bromide and phenacyldimethylsulfonium bromide and m-nitro and p-methyl derivatives of each of these salts with a variety of p-substituted benzene diazonium chlorides provide a simple method for synthesising 1,4 - dihydro - 1,2,4,5 - tetrazines in fairly good yields. The reaction appears to proceed via the nitrilimine intermediate which dimerises to yield the desired tetrazines. The structures of the tetrazines were established on the basis of elemental analysis and IR and NMR spectral data. An attempt has also been made to explain the relative reactivity of the three types of ylides.

4.2. INTRODUCTION :

The chemistry of pyridinium, phosphonium and sulfonium salts and their ylides has attracted a great deal of attention on account of their important synthetic applications.^{1,2} They have been utilised in the synthesis of cyclopropanes,¹ 2-arylindoles,^{3,4} epoxides⁵ and aziridines.⁶ However, almost no sincere attempt has been made to

synthesise tetrazines by using the ylides.

Huisgen et al⁷ reported the synthesis of 1,4 - dihydro - 1,2,4,5 - tetrazines by the thermolysis of 2,5 - disubstituted tetrazoles and suggested that nitrilimine intermediate was involved.⁸ However, the reaction course of thermolysis was not specific and a number of side products were formed. The reaction of phenylhydrazones of α - chlorobenzaldehyde^{9,10} and α - chloroglyoxylic acid¹¹ with a base also gives 1,4 - dihydro - 1,2,4,5 - tetrazines; but in this case too the yield is unsatisfactory. Pyridinium and arsonium salts have been successfully used to synthesise such tetrazines. The reaction involves the interaction of phenacylpyridinium bromide or phenacyltriphenylarsonium bromide with benzene diazonium salts in presence of sodium acetate in methanol at 0°C. The reaction appears to proceed via 1,3 - dipolar dimerization of the intermediate nitrilimine which is, in turn, formed by the attack of the carbanion of the in situ generated ylide on diazonium cation.

In the present chapter, investigations on the reactions of substituted phenacylpyridinium bromides, phenacyltriphenylphosphonium bromides and phenacyldimethylsulfonium bromides with a wide variety of aryl diazonium salts have been reported. The investigations were carried out with a view to test and compare the domain of applicability of

the salts of the three types of ylides for the synthesis of 1,4 - dihydro - 1,2,4,5 - tetrazines.

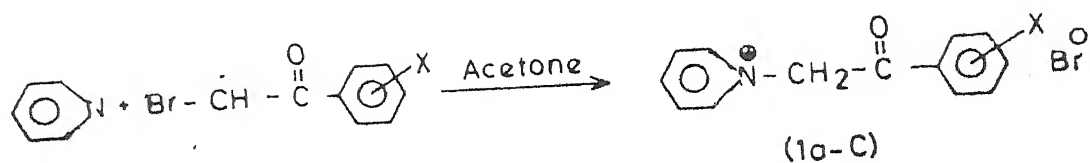
4.3. RESULTS AND DISCUSSION :

The reaction of phenacyl bromide, *m*-nitrophenacyl bromide or *p*-methylphenacyl bromide with pyridine in acetone at the room temperature gave corresponding substituted pyridinium bromides (1a-c) in good yields (Scheme IV.1). The structures of these salts (1a-c) were supported by the compatibility of their m.p. to those reported in literature¹²⁻¹⁴ and also on the basis of spectral studies. The IR (KBr) spectra of the salts showed a strong band around 1670-1690 cm^{-1} due to the stretching vibrations of the C = O group. The NMR (CDCl_3) spectra showed a sharp singlet in the range 5.00 - 5.44 due to the presence of methylene protons adjacent to nitrogen atom. The aromatic protons were absorbed in the range of δ 7.25-8.40.

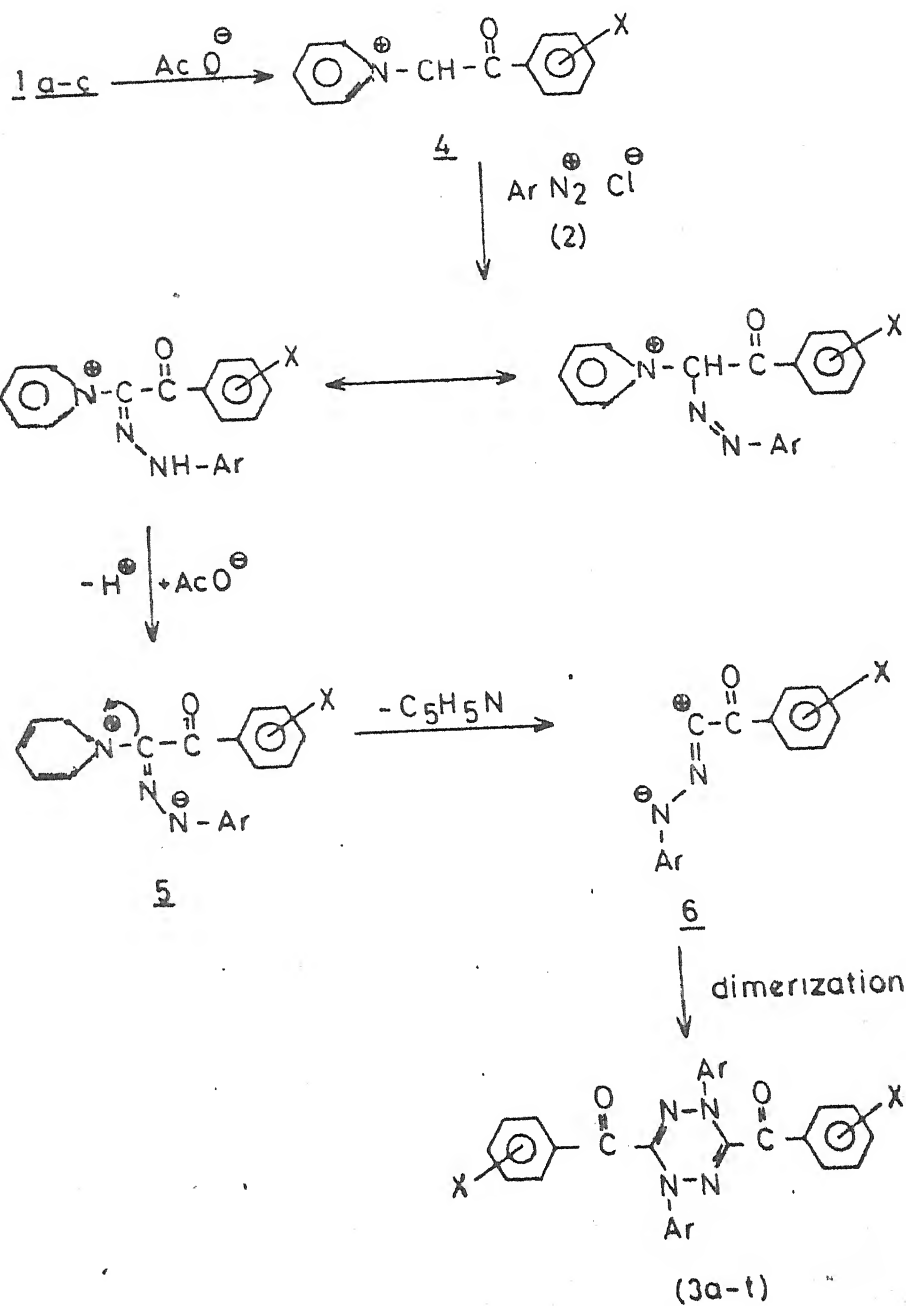
Reactions of salts (1a-c) with different aromatic diazonium salts (2) in methanol at 0°C in presence of sodium acetate gave corresponding 1,4 - diaryl -3,6 - diaroyl - 4,4 - dihydro -1, 2,4,5 - tetrazines (3a-t) in 50-78% yields (Scheme IV.2) (Route A).

The reaction of phenacyl bromide, *m*-nitrophenacyl bromide or *p*-methylphenacyl bromide with triphenylphosphine

Scheme IV.1



Scheme IV.2

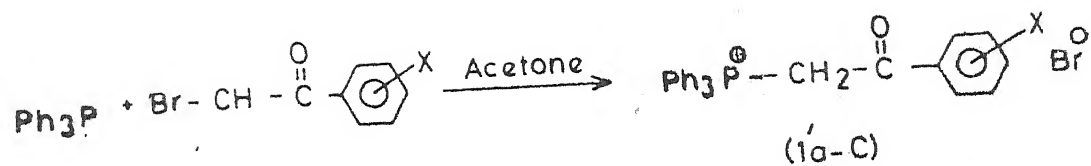


at the room temperature gave the corresponding substituted phosphonium bromides (1'a-c) in each case (Scheme IV.3). The structures of these salts were in broad agreement with those reported in literature¹⁵⁻¹⁷ as indicated by their m.p. and spectral studies. The IR(KBr) spectra of these salts showed a strong band around 1680-1690 cm^{-1} due to the stretching vibrations of the $\text{C}=\text{O}$ group. A sharp singlet in the range δ 5.00-5.45 revealed the methylene protons adjacent to the P atom. The aromatic protons were absorbed in the range δ 7.25-8.40.

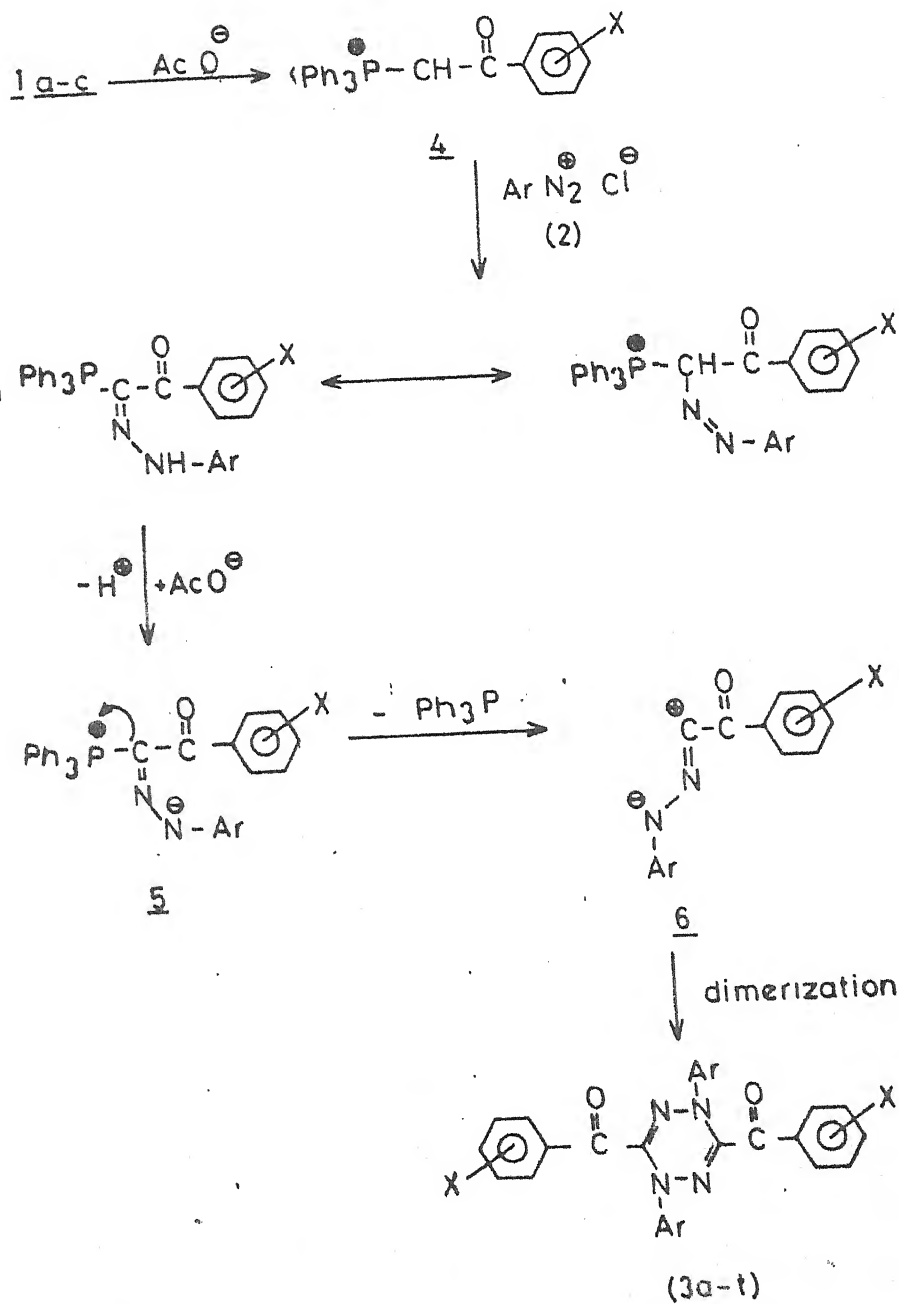
Reactions of the salts (1'a-c) with various diazonium salts (2) in methanol at 0°C in presence of sodium acetate gave the corresponding 1,4 - diaryl - 3,6 - diaroyl - 1,4 - dihydro - 1,2,4,5 - tetrazines (3a-t) in 45 to 70% yields (Scheme IV.4) (Route B).

The overall picture for substituted sulfonium salts is quite similar to that of substituted pyridinium and phosphonium salts. Thus, the reaction of phenacyl bromide, m-nitrophenacyl bromide or p-methylphenacyl bromide with dimethylsulfide in acetone at the room temperature gave corresponding substituted phenacyldimethylsulfonium bromides (1''a-c) in fair to good yields (Scheme IV.5). The structures of these salts were supported on the basis of compatibility of their m.p. to those reported in literature¹⁸⁻²⁰ and also

Scheme IV.3



Scheme IV.4



on the basis of their spectral studies. The IR(KBr) spectra showed a strong band in the region $1670-1690\text{ cm}^{-1}$ due to the stretching vibrations of the $\text{C}=\text{O}$ group. The NMR(CDCl_3) spectra showed a singlet around δ 3.02-3.20 due to two methyl groups directly attached to the sulfonium group. In each case, a sharp singlet in the range δ 5.00-5.45 revealed the methylene protons adjacent to the sulfonium group. The aromatic protons were visible in the range δ 7.25-8.40.

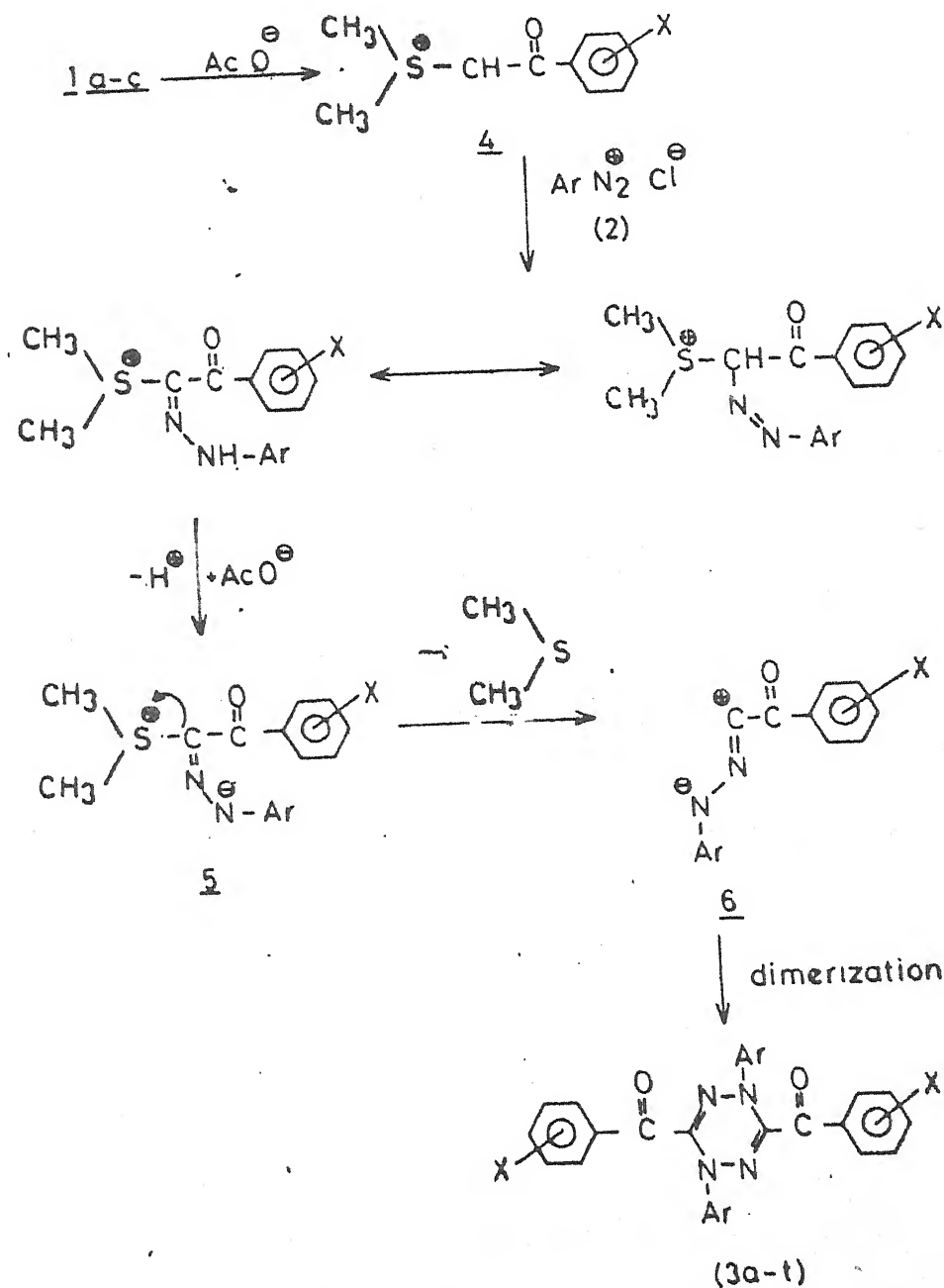
Reactions of salts ($1^{\text{a-c}}$) with different aromatic diazonium salts (2) in methanol at 0°C in presence of sodium acetate gave, in each case, the corresponding 1,4 - diaryl-3,6 - diaroyl - 1,4 - dihydro - 1,2,4,5 - tetrazines in 50-70% yields (Scheme IV.6) (Route C).

The reactions of aryldiazonium salts (2) with phenacylpyridinium and phenacyldimethylsulfonium bromides have been reported. It has been suggested that the diazonium salt reacts directly with pyridinium phosphonium or sulfonium salts to give the ylides. But the suggestion appears to be contrary to observations of Huisgen et al^{7,8,9}. The diazonium salt, being electrophilic in nature, would be expected to react with nucleophilic species and therefore, it seems more probable that the salt would first be converted into the corresponding ylide which would then react with the diazonium salt(2). The reaction of (2) with the ylide

Scheme IV.5



Scheme IV.6



instead of the salt appears to reflect the situation in our investigations. Thus, on stirring the corresponding salt solution with sodium acetate, appearance of characteristic colouration indicated the generation of the respective ylide (4). When the diazonium salt solution (2) is added to the ylide solution, the acetate ion, being a stronger base than the ylide, neutralises the excess of the acid present in the diazonium salt solution and the ylide is left to interact with the diazonium salt to yield the species (5). The latter subsequently changes into nitrilimine (6) which finally undergoes 1,3 - dipolar - dimerisation to form 1,4 - dihydro - 1,2,4,5 - tetrazines (3a-t). The course of reaction is depicted in schemes IV.2, IV.4 and IV.6. The reactions of pyridinium, phosphonium and sulfonium salts (1a-c, 1'a-c and 1''a-c) with α - and β - naphthyldiazonium salts were also attempted. However, the yield was very poor and pure products could not be isolated. The low yields in such cases may be attributed to steric hinderance by bulky naphthyl groups.

All the tetrazines (3a-t), the common products of reactions of pyridinium, phosphonium and sulfonium ylides with aromatic diazonium salts, were characterised on the basis of IR and NMR spectra. In the IR spectra, a sharp peak in the region of 1670-1640 cm^{-1} was attributed to C = O stretching frequency (Table IV.2). In the NMR spectra

only a multiplet was observed in the region δ 6.8-8.2 ppm corresponding to aromatic protons (Table IV.3). The physical data of the 1,4-dihydro- 1,2,4,5 -tetrazines (3a-t) is summarised in table IV.1.

The extent of quantitative yields of tetrazine derivatives (3a-t) by the reactions of pyridinium (1a-c) (Route A), phosphonium (1'a-c) (Route B) and sulfonium (Route C) salts may be used to make some empirical generalisations regarding the comparative reactivity and stability of the corresponding ylides. The order of reactivity on the basis of extent of yields of the tetrazine derivatives may be characterised as pyridinium ylides > sulfonium ylides > phosphonium ylides.

The pyridinium or the cycloimmonium ylides are the most reactive among the three types under investigation. Their greater reactivity may be attributed to their greater nucleophilicity due to total lack of $d\pi - p\pi$ bonding. In the case of sulfonium and phosphonium ylides, $d\pi - p\pi$ bonding may occur to a considerable extent to favour the ylene form which has reduced nucleophilic character resulting in lesser reactivity and hence lesser yields of tetrazine derivatives.

Although both sulfonium ylides and phosphonium ylides are characterised by $d\pi - p\pi$ bonding, the former are more reactive probably due to the presence of methyl

groups which renders them more nucleophilic compared to phosphonium ylides with three phenyl groups. The comparatively greater resonance stabilization due to the three phenyl groups and greater steric hinderance offered by them may probably account for the greater stability and hence lesser reactivity of phosphonium ylides vis-a-vis the sulfonium ylides.

4.4. EXPERIMENTAL :

All the starting materials of A.R. grade were obtained from commercial sources (BDH, S. Merck, E. Merck, SISCO etc.). The amines used for the preparation of diazonium salts (2) were purified either by distillation or by recrystallisation. The diazonium salts were prepared by diazotisation of aromatic primary amines with NaNO_2 and HCl (dilute) at $0-5^\circ\text{C}$ as reported in literature.^{21,22}

1. Diazotization of aromatic primary amines :

Substituted aniline (5 ml) in a mixture of Conc. HCl (16 ml) and water (16 ml) was taken in a round bottom flask and cooled to 0°C . A mixture of sodium nitrite (4 gm) in water (20 ml) was added dropwise with constant stirring while maintaining the temperature of the mixture below 5°C . The reactions of these diazonium salts were carried out in situ.

II. Preparation of substituted phenacyl pyridinium(1a-c), triphenylphosphinium (1'a-c) and dimethylsulfonium (1''a-c) bromides:

General Procedure :

A solution of 250 m mole of the substituted phenacyl bromide and 250 m mole of pyridine (or triphenylphosphine or dimethylsulfide) in 250 m mole of anhydrous acetone was stirred for 6-8 hours at the room temperature. A solid mass was precipitated. It was filtered and washed twice with acetone and recrystallised from benzene/petroleum ether to get the crystalline final product.

The above procedure was used to prepare the following salts:

i. Phenacylpyridinium bromide(1a): Pale yellow crystals, m.p. 192-93°C (Lit.¹² m.p. 195-97°C) IR(KBr) 1690 cm^{-1} ($\nu_{\text{C}=\text{O}}$)

ii. m-nitrophenacylpyridinium bromide(1b): Pale yellow crystals, m.p. 220-22°C (Lit.¹³ m.p. 225°C), IR(KBr) 1515 and 1552 cm^{-1} ($\nu_{\text{C}-\text{NO}_2}$); 1680 cm^{-1} ($\nu_{\text{C}=\text{O}}$).

iii. p-methylphenacylpyridinium bromide(1c): Light reddish crystals, m.p. 200-202°C (Lit.¹⁴ m.p. 203-204°C) IR(KBr) 1670 cm^{-1} ($\nu_{\text{C}=\text{O}}$).

iv. Phenacyltriphenylphosphonium bromide (1'a): white crystals

m.p. 279-80

(Lit.¹⁵ m.p. 281-82°C); IR(KBr) 1680 cm^{-1} ($\nu_{\text{C=O}}$)

v. m-nitrophenacyltriphenylphosphonium bromide(1'b): Orange

yellow

crystals, m.p. 218-19°C (Lit.¹⁶ m.p. 216-17°C)

IR(KBr) 1680 cm^{-1} ($\nu_{\text{C=O}}$), 1550-1510 cm^{-1} ($\nu_{\text{C-NO}_2}$)

vi. p-methylphenacyltriphenylphosphonium bromide(1'c): Pale

yellow

crystalline solid, m.p. 260-262°C (Lit.¹⁷ m.p. 262-63°C)

IR(KBr) 1690 cm^{-1} ($\nu_{\text{C=O}}$)

vii. Phenacyldimethylsulfonium bromide (1"a): white crystalline

solid, m.p.

138-40°C (Lit.¹⁸ m.p. 140°C); IR(KBr) 1680 cm^{-1} ($\nu_{\text{C=O}}$)

viii. m-nitrophenacyldimethylsulfonium bromide(1"b): Orange

yellow

crystals, m.p. 148-50°C (Lit.¹⁹ m.p. 152-53°C).

IR(KBr) 1690 cm^{-1} ($\nu_{\text{C=O}}$), 1515 and 1550 cm^{-1} ($\nu_{\text{C-NO}_2}$)

ix. p-methylphenacyldimethylsulfonium bromide(1"c): Pale

yellow

crystals, m.p. 132-134°C (Lit.²⁰ m.p. 132°C).

IR(KBr) 1675 cm^{-1} ($\nu_{\text{C=O}}$)

III. Reaction of substituted phenacylpyridinium (1a-c),
-triphenylphosphonium (1'a-c) and -dimethylsulfonium
(1''a-c) bromides with aryldiazonium salts (2):

General procedure :

A mixture of the salt (1a-c, 1'a-c or 1''a-c) (10m mole in 50 ml of methanol) and sodium acetate (50m mole in 20 ml of water) was cooled on an ice bath and stirred whereupon a characteristic colour developed. A separately prepared diazonium salt solution (10m mole) was added and the mixture was kept on an ice bath for 3-6 hours. The solid mass, which got separated, was filtered and recrystallised from an appropriate solvent to yield the desired tetrazine derivative.

TABLE IV. A

PHYSICAL PROPERTIES OF 1,4-DIHYDRO-1,2,4,5-TETRAZINES

Comp- ound	X	Ar	Yield %	m.p. °C	Lit.m.p. °C	Route	Analytical data found(Cald) %		
							C	H	N
1	2	3	4	5	6	7	8	9	10
3a	H	C ₆ H ₅	78	194	196	A	75.62	4.51	12.52
			58			B	75.69	4.48	12.57
			64			C	75.61 (75.66)	4.50 (4.54)	12.51 (12.60)
3b	H	p-MeC ₆ H ₄	75	146	148	A	76.26	5.11	11.84
			55			B	76.28	5.13	11.78
			66			C	76.23 (76.25)	5.10 (5.11)	11.80 (11.86)
3c	H	p-Cl C ₆ H ₄	70	200	202	A	65.46	3.48	10.88
			65			B	65.50	3.47	10.92
			65			C	65.52 (65.49)	3.52 (3.50)	10.90 (10.91)

1	2	3	4	5	6	7	8	9	10
3d	H	p-NO ₂ C ₆ H ₄	70	215	217	A	62.93	3.38	15.75
			56			B	62.94	3.41	15.70
			60			C	62.90	3.38	15.72
							(62.92)	(3.39)	(15.72)
3e	H	p-Br C ₆ H ₄	75	187	186	A	55.84	3.91	9.26
			60			B	55.82	3.03	9.25
			64			C	55.82	2.96	9.28
							(55.81)	(2.99)	(9.30)
3f	H	p-Br C ₆ H ₄	68	177	176	A	48.20	2.53	8.02
			65			B	48.26	2.59	8.10
			68			C	48.24	2.56	8.12
							(48.27)	(2.58)	(8.04)
3g	H	p-MeO C ₆ H ₄	60	160	158	A	71.40	4.76	11.08
			56			B	71.45	4.81	11.12
			58			C	71.38	4.80	11.15
							(71.42)	(4.79)	(11.10)

1	2	3	4	5	6	7	8	9	10
3h	H	p-Eto C ₆ H ₄	65	151	150	A	72.15	5.25	10.56
			32			B	72.12	5.29	10.48
			40			C	72.14	5.21	10.53
							(72.18)	(5.26)	(10.52)
3i	m-NO ₂	C ₆ H ₅	68	184-85	183	A	62.88	3.39	15.70
			50			B	62.95	3.36	15.78
			60			C	62.98	3.33	15.74
							(62.92)	(3.36)	(15.72)
3j	m-NO ₂	p-NO ₂ C ₆ H ₄	50	194	197	A	53.80	2.54	17.99
			40			B	53.78	2.53	17.93
			48			C	53.88	2.59	17.90
							(53.84)	(2.56)	(17.94)
3k	m-NO ₂	p-Cl C ₆ H ₄	56	151	154	A	56.47	2.68	13.90
			54			B	56.57	2.62	13.98
			54			C	56.55	2.62	13.92
							(56.52)	(2.65)	(13.93)

1	2	3	4	5	6	7	8	9	10
31	m-NO ₂	p-Me C ₆ H ₄	66	176	178	A	64.09	3.87	14.86
			60			B	64.02	3.99	14.90
			62			C	64.00	3.91	14.96
							(64.05)	(3.94)	(14.94)
3m	m-NO ₂	p-MeO C ₆ H ₄	70	145-47	148	A	60.65	3.78	14.19
			60			B	60.55	3.76	14.08
			66			C	60.60	3.70	14.10
							(60.61)	(3.73)	(14.14)
3n	m-NO ₂	p-Br C ₆ H ₄	55	172-174	173	A	48.51	2.36	12.16
			45			B	48.58	2.28	12.18
			50			C	48.52	2.34	12.10
							(48.55)	(2.31)	(12.13)
3o	m-NO ₂	p-I C ₆ H ₄	50	208	210	A	42.70	2.00	10.65
			35			B	42.68	2.06	10.66
			40			C	42.71	2.04	10.70
							(42.74)	(2.03)	(10.69)

1	2	3	4	5	6	7	8	9	10
3p	p-CH ₃	C ₆ H ₅	66	213-20	216	A	76.30	5.08	11.90
			60			B	76.28	5.10	11.82
			58			C	76.26	5.14	11.85
							(76.25)	(5.12)	(11.86)
3q	p-CH ₃	p-NO ₂ C ₆ H ₄	70	184	186	A	68.02	3.90	14.99
			66			B	64.06	3.91	14.96
			60			C	64.07	3.96	14.90
							(64.05)	(3.94)	(14.94)
3r	p-CH ₃	p-Cl C ₆ H ₄	45	168	170	A	66.52	4.09	10.32
			40			B	66.55	4.02	10.37
			40			C	66.57	4.07	10.30
							(66.54)	(4.06)	(10.35)
3s	p-CH ₃	p-Me C ₆ H ₄	56	158	158	A	76.38	5.62	11.18
			53			B	76.32	5.58	11.22
			50			C	76.78	5.52	11.24
							(76.30)	(5.60)	(11.20)

1	2	3	4	5	6	7	8	9	10
3t	p-CH ₃	p-Br C ₆ H ₄	62	202	200	A	56.31	3.53	8.81
			54			B	56.34	3.45	8.86
			50			C	56.28	3.47	8.91
							(57.30)	(3.49)	(8.88)

TABLE IV.2

IR SPECTRAL DATA OF 1,4-DIHYDRO-2,4,5-TETRAZINES (3a-t)

Compound	IR Data (KBr) cm^{-1}				
	$\nu_{\text{C-H}}$	$\nu_{\text{C=C}}$	$\phi_{\text{C-H}}$	$\nu_{\text{C=N}}$	$\nu_{\text{C=O}}$
4a	3145	1610	998	1510	1670
4b	3135	1608	985	1515	1665
4c	3165	1618	995	1505	1665
4d	3145	1608	988	1518	1660
4e	3140	1610	990	1512	1665
4f	3155	1615	992	1510	1645
4g	3148	1605	995	1512	1648
4h	3168	1596	990	1508	1645
4i	3138	1595	985	1500	1640
4j	3128	1620	989	1510	1652
4k	3155	1605	1005	1508	1665
4l	3120	1600	995	1512	1650
4m	3135	1602	998	1518	1658
4n	3160	1620	995	1505	1645
4o	3132	1608	992	1510	1648
4p	3148	1605	995	1515	1670
4q	3160	1595	990	1505	1665
4r	3155	1598	998	1508	1650
4s	3150	1615	988	1502	1655
4t	3145	1605	995	1505	1650

ν = Stretching vibration, ϕ = out of plane deformation
of hydrogen attached to
C=C

TABLE IV.3

NMR SPECTRAL DATA OF 1,4 -DIHYDRO- 1,2,4,5-TETRAZINES(3a-t)

Comp- ound	NMR(CDCl ₃) data δ (ppm)	No. of H	Assignment
4a	6.40-8.20, m	20H	ArH
4b	2.25, s	6H	CH ₃
	6.10-8.25, m	18H	ArH
4c	6.40-8.20, m	18H	ArH
4d	6.50-8.50, m	18H	ArH
4e	6.30-8.35, m	18H	ArH
4f	6.28-8.25, m	18H	ArH
4g	3.50, s	6H	OCH ₃
	6.20-8.20	18H	ArH
4h	4.25, q	4H	CH ₂
	1.55, t	6H	CH ₃
	6.10-8.20	18H	ArH
4i	6.50-8.35, m	18H	ArH
4j	6.55-8.38, m	16H	ArH
4k	6.45-8.20, m	16H	ArH
4l	2.35, s	6H	CH ₃
	6.40-8.25, m	16H	ArH
4m	3.70, s	6H	OCH ₃
	6.35-8.10, m	16H	ArH
4n	6.48-8.28, m	16H	ArH
4o	6.35-8.05, m	16H	ArH

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Comp- ound	NMR(CDCl ₃) data δ (ppm)	No. of H	Assignment
4p	2.35, s	6H	CH ₃
	6.25-8.15, m	16H	ArH
4q	2.45, s	6H	CH ₃
	6.45-8.30, m	16H	ArH
4r	2.38, s	6H	CH ₃
	6.35-8.20, m	16H	ArH
4s	2.32, s	12H	CH ₃
	6.25-8.25, m	16H	ArH
4t	2.42, s	6H	CH ₃
	6.35-8.25, m	16H	ArH

s = singlet, q = quartet, t = triplet,
m = multiplet.

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CHAPTER - V

METAL YLIDE COMPLEXES : MERCURY (II), CADMIUM (II),
COBALT(II) AND NICKEL (II) COMPLEXES OF SUBSTITUTED
PHENACYLIDINE-PYRIDINIUM,-TRIPHENYL PHOSPHONIUM AND
-DIMETHYLSULFONIUM YLIDES

METAL YLIDE COMPLEXES : MERCURY (II), CADMIUM (II),
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PHENACYLIDINE-PYRIDINIUM, -TRIPHENYL PHOSPHONIUM AND
-DIMETHYLSULFONIUM YLIDES

5.1. ABSTRACT :

The mercury (II), cadmium (II), cobalt (II) and nickel (II) halide complexes with phenacylidinepyridinium, 4-chlorophenacylidinepyridinium, 4-methylphenacylidinepyridinium and 4-methoxyphenacylidinepyridinium ylides and their phosphonium and sulfonium analogues have been prepared. The presence of the ylide ions as non-coordinated counter ions is deduced from IR spectral data. The $\nu(\text{C}=\text{O})$ frequencies are high relative to those of the free ylides and are nearer to those of the completely protonated onium salts to indicate that coordination occurs via methine carbon atoms. The structures of the resulting complexes were elucidated on the basis of elemental and IR data.

5.2. INTRODUCTION :

The synthetic potential of ylides appears to have been extensively studied¹⁻⁶. But the metalation reactions of the ylides are few and far between although ever since the initiation¹ of work on metalation of ylides in 1965, ylides have been considered as versatile ligands capable of coordinating with metals in their various oxidation states

to form some useful chelates and complexes⁷⁻¹⁰. A few such studies carried out so far have indicated a great deal of potential due to marked stability of the metal ylide complexes. The ylides essentially differ from other organic ligands in that the former coordinate with metal halides as neutral ligands to form a sigma bond through the ylide carbon.

Earlier only preliminary studies⁷ of inorganic components with ylides were reported. Investigators then took on themselves to unravel the fascinating world of this newly emerging branch of organometallic chemistry. Reactions of ylides with boron, aluminium,^{11,12} mercury^{13,14} and tin compounds have been reported in the recent years. There have also been some reports on the reactions of ylides with transition metals.¹⁵⁻¹⁹ The studies of metallate complexes containing co-ordinating ylides are also very rare so far.¹⁸⁻²⁰ It is therefore obvious that there is still great scope for the study of metalation reactions of ylides with transition metals.

It is apparent that the work in the field has just begun. There is sure promise of great potential for the ylide metallate complexes are characterised by greater stability than their parent ylides. It is in this context that it was thought worthwhile to extend this type of studies to prepare metallate complexes of mercury (II), cadmium (II), cobalt (II) and nickel (II) with substituted phenacylidine -

pyridinium, triphenylphosphonium and dimethylsulfonium ylides.

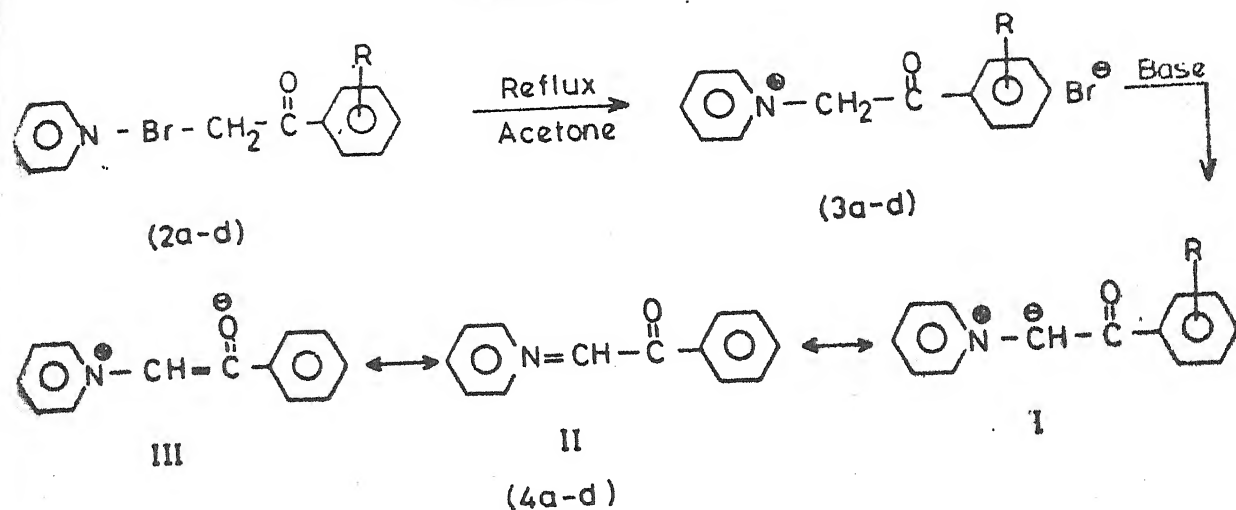
5.3. RESULTS AND DISCUSSION :

Pyridine (1) reacts with phenacyl bromide (2a), 4-chlorophenacyl bromide (2b), 4-methylphenacyl bromide (2c) and 4-methoxyphenacyl bromide (2d) in acetone at the reflux temperature to form the corresponding substituted phenacylpyridinium bromide (3a-d). These salts (3a-d), on treatment with aqueous NaOH, yield the corresponding ylides (4a-d) (Scheme V.1). The identification of these ylides is based on IR spectral data (Table V.1).

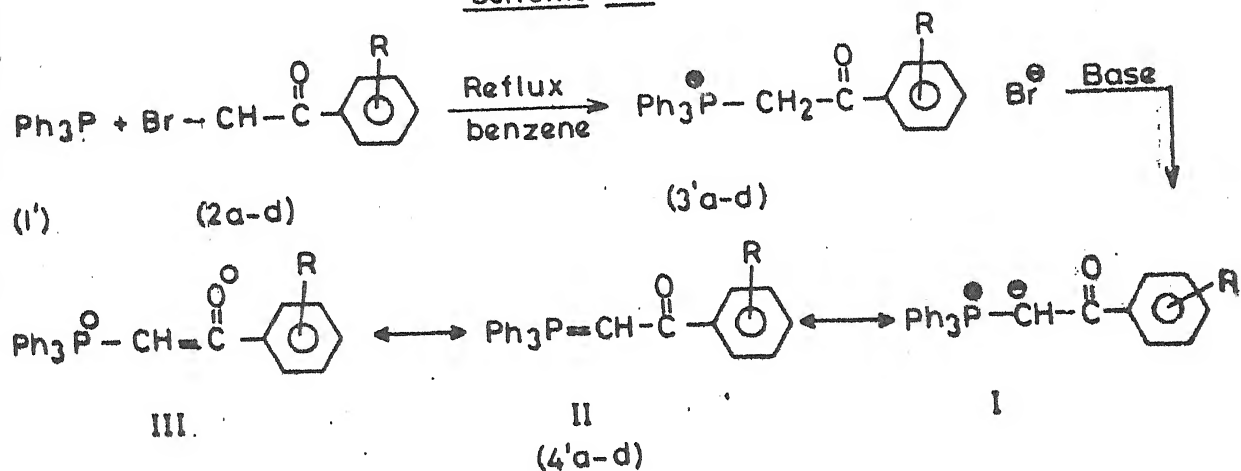
On the lines similar to the preparation of substituted phenacylidinepyridinium ylides (4a-d), triphenylphosphine (1') and dimethylsulfide (1'') were reacted with (2a-d) in acetone leading to the formation of the corresponding substituted phenacylphosphonium (3'a-d) and sulfonium (3''a-d) salts which when treated with aqueous NaOH formed the ylides (4'a-d and 4''a-d) (Scheme V.2 and V.3). The identification of these ylides and their salts was also based on IR spectral data (Table V.2 and V.3).

The reaction of the ylides (4a-d, 4'a-d and 4''a-d) with the halides of mercury (II), cadmium (II), cobalt (II) and nickel (II) (MX_2 where M = metal and X = halogen) in methanol gave a series of metal halide complexes (6a-q,

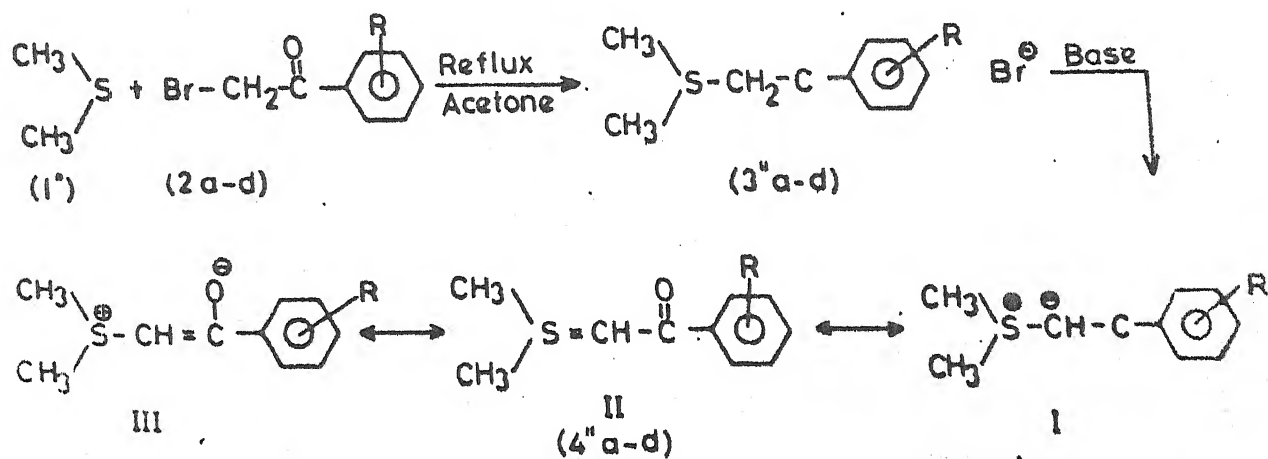
Scheme V.1



Scheme V.2



Scheme V.3

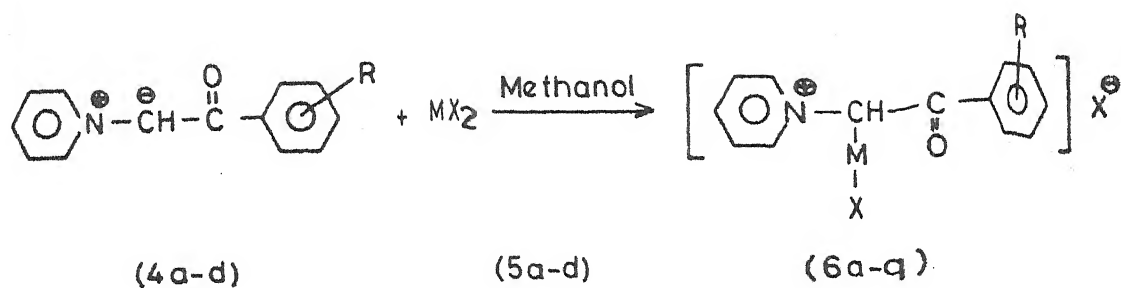


6'a-q and 6" a-q) in varying yields. The metal halide complexes $[M_2(Ylide)_2X_4]$ presumably contain a bridging X^- group (Scheme V.4, V.5 and V.6).

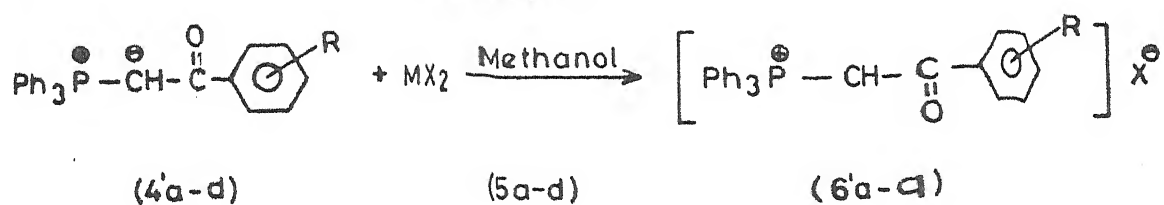
Electron donating substituents of the phenyl ring of the ylides increase the ease of complex formation as judged by the yields of the final products (6a-q, 6'a-q and 6" a-q).

The metalation reaction seems to proceed via the intermediate ylide carbanion. The ylides used for the reactions may be represented by the three canonical forms I-III (Scheme V.1, V.2 and V.3). The values of carbonyl stretching frequencies observed for the ylides (4a-d, 4'a-d and 4" a-d) reveal an important contribution of the enolate structure III. In this structure the lone pair of electrons formally on the ylidic carbanion is considered to be delocalised to a large extent. Thus, the ylides have two possible coordination sites towards the metal halide; carbonyl oxygen which would result in low frequency shift of $\nu(C=O)$ owing to increased enolate character (Cf the form III) and nucleophilic methine carbon which would result in high frequency shift of $\nu(C=O)$ due to increased carbonyl character (Cf the form I). The $\nu(C=O)$ bands of the complexes were, in fact, formed at higher frequencies than the original ylides. Co-ordination through methylene carbon is thus established. In general, the analytical data of the

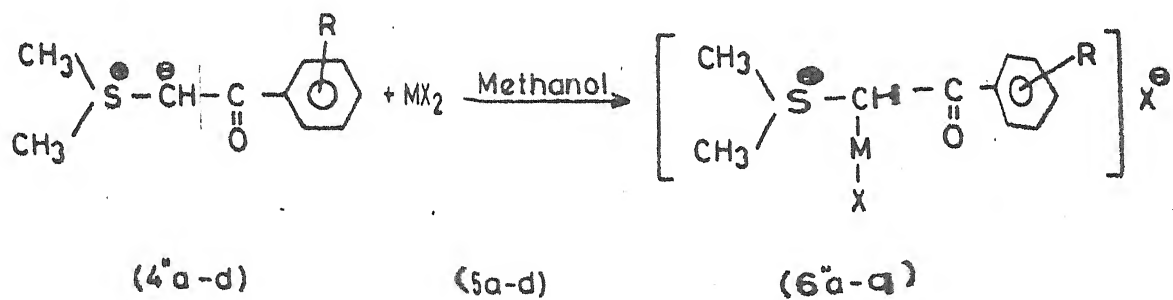
Scheme V.4



Scheme V.5



Scheme V.6



complexes were found to be in fairly good agreement with indicated formulations. But one can not rule out the presence of small amounts of the other salts which might be expected in view of high halide mobility likely to be encountered in these systems. Elemental analysis indicated that the complexes were 1:1 adducts probably dinuclear with halide bridging. Tables V.4, V.5 and V.6 include the structure and physical properties of metal halide complexes (6a-q, 6'a-q and 6''a-q respectively).

5.4. EXPERIMENTAL :

All reagents were obtained from commercial sources (BDH, S.Merck, E.Merck, SISCO etc.). Starting materials were prepared by following standard methods. Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer Infracord instrument.

1. Synthesis of metal-ylide complexes(6a-q, 6'a-q and 6''a-q):

General procedure :

A solution of the metal halide (1.0 m mole) in methanol (20 ml) was added dropwise to the solution of substituted phenacylidine ylide (4a-d, 4'a-d and 4''a-d) (2.0 m mole) in methanol (20 ml). Immediately after the complete addition, a precipitate began to form rapidly. The mixture was stirred for further two hours at the room

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temperature and the solid was then filtered off, washed with methanol and diethyl ether and dried in vacuo over calcium sulfate.

TABLE V.1IR SPECTRAL DATA FOR 6a-q

Product	IR data (KBr) ν (cm ⁻¹)		
	Aromatic C-H	C=O	C-M
6a	3400	1680	725
6b	3300	1685	690
6c	3600	1630	700
6d	3300	1685	685
6e	3400	1645	695
6f	3400	1650	715
6g	3410	1655	705
6h	3520	1680	745
6i	3410	1690	725
6j	3510	1640	720
6k	3600	1645	725
6l	3420	1640	760
6m	3410	1650	730
6n	3610	1635	720
6o	3520	1640	740
6p	3560	1690	700
6q	3520	1685	720

TABLE V.2IR SPECTRAL DATA FOR 6'a-g

Product	IR data (KBr) ν (cm ⁻¹)		
	Aromatic C-H	C=O	C-M
6'a	3920	1675	730
6'b	3310	1675	700
6'c	3600	1620	690
6'd	3320	1650	680
6'e	3400	1635	690
6'f	3410	1640	710
6'g	3420	1650	710
6'h	3520	1675	750
6'i	3400	1680	720
6'j	3500	1635	720
6'k	3600	1640	725
6'l	3390	1635	765
6'm	3380	1645	735
6'n	3560	1630	725
6'o	3520	1630	750
6'p	3550	1630	710
6'q	3500	1680	740

TABLE V.3

IR SPECTRAL DATA FOR 6^aa-q

Product	IR data (KBr) ν (cm ⁻¹)		
	Aromatic C-H	C=O	C-M
6 ^a a	3400	1665	720
6 ^a b	3300	1665	710
6 ^a c	3600	1610	680
6 ^a d	3320	1640	690
6 ^a e	3400	1625	700
6 ^a f	3400	1630	700
6 ^a g	3400	1635	720
6 ^a h	3500	1665	740
6 ^a i	3400	1670	710
6 ^a j	3500	1620	720
6 ^a k	3600	1620	730
6 ^a l	3400	1625	760
6 ^a m	3400	1630	740
6 ^a n	3600	1620	730
6 ^a o	3500	1620	750
6 ^a p	3550	1665	720
6 ^a q	3500	1660	730

TABLE V.4

STRUCTURE AND PHYSICAL PROPERTIES OF METAL YLIDE COMPLEXES(6a-q)

Product	M	X	R	m.p. °C	Yield %	Elemental analysis: Found/Calcd %		
						C	H	X
1	2	3	4	5	6	7	8	9
6a	Hg	Cl	H	180-81	60	33.96 (34.02)	2.42 (2.39)	15.43 (15.48)
6b	Hg	Br	H	154-56	66	28.45 (28.49)	2.04 (2.01)	29.15 (29.22)
6c	Cd	Cl	H	184-85	64	42.02 (42.11)	3.01 (2.97)	19.10 (19.17)
6d	Ni	Cl	H	148-49	63	49.29 (49.37)	3.42 (3.47)	22.47 (22.42)
6e	Co	Cl	H	142-43	65	49.28 (49.21)	3.46 (3.47)	22.42 (22.39)
6f	Hg	Cl	4-CH ₃	169-70	70	35.52 (35.55)	2.71 (2.75)	15.07 (15.02)
6g	Hg	Br	4-CH ₃	167-68	75	29.86 (29.91)	2.25 (2.31)	28.56 (28.56)
6h	Cd	Cl	4-CH ₃	248	65	43.62 (43.70)	3.42 (3.38)	18.54 (18.47)

1	2	3	4	5	6	7	8	9
6i	Cd	I	4-CH ₃	121-22	60	29.73 (29.61)	2.26 (2.29)	44.80 (44.76)
6j	Ni	Cl	4-CH ₃	143-44	64	50.72 (50.80)	3.88 (3.93)	21.50 (21.47)
6k	Co	Cl	4-CH ₃	195-96	60	50.67 (50.75)	3.88 (3.92)	21.49 (21.45)
6l	Hg	Cl	4-OCH ₃	163-64	70	34.37 (34.38)	2.60 (2.66)	14.55 (14.53)
6m	Hg	Br	4-OCH ₃	160-61	70	29.11 (29.08)	2.20 (2.25)	27.68 (27.70)
6n	Cd	I	4-OCH ₃	230-32	70	41.90 (41.96)	3.21 (3.25)	17.70 (17.73)
6o	Cd	I	4-OCH ₃	153-54	75	28.80 (28.79)	2.20 (2.23)	43.50 (43.54)
6p	Hg	Cl	4-Cl	160-61	65	31.60 (31.60)	2.01 (2.03)	21.45 (21.60)
6q	Hg	Br	4-Cl	135-36	60	26.84 (26.80)	1.68 (1.71)	27.48 (27.49)

TABLE V.5

STRUCTURE AND PHYSICAL PROPERTIES OF METAL-YLIDE
COMPLEXES (6'a-g)

Pro- duct	M	X	R	m.p. °C	Yield %	Elemental analysis found (Calcd) %		
						C	H	X
1	2	3	4	5	6	7	8	9
6'a	Hg	Cl	H	162-63	50	47.81 (47.86)	3.19 (3.22)	10.96 (10.90)
6'b	Hg	Br	H	153-54	55	42.18 (42.13)	2.79 (2.83)	21.62 (21.60)
6'c	Cd	Cl	H	165-66	50	55.46 (55.38)	3.68 (3.72)	12.51 (12.60)
6'd	Ni	Cl	H	135	50	61.18 (61.21)	4.14 (4.12)	13.82 (13.93)
6'e	Co	Cl	H	123-24	45	61.12 (61.18)	4.08 (4.11)	13.88 (13.92)
6'f	Hg	Cl	4-CH ₃	140-42	55	48.60 (48.65)	3.40 (3.45)	10.51 (10.67)
6'g	Hg	Br	4-CH ₃	138-39	60	42.88 (42.92)	3.02 (3.05)	21.17 (21.20)
6'h	Cd	Cl	4-CH ₃	210-11	50	56.15 (56.11)	3.92 (3.98)	12.26 (12.30)

1	2	3	4	5	6	7	8	9
6'i	Od	I	4-CH ₃	109-10	50	42.56 (42.61)	3.11 (3.02)	33.47 (33.40)
6'j	N1	Cl	4-CH ₃	130-31	52	61.82 (61.87)	4.46 (4.39)	13.52 (13.56)
6'k	Co	Cl	4-CH ₃	182-83	45	61.76 (61.83)	4.32 (4.38)	13.59 (13.55)
6'l	Hg	Cl	4-OCH ₃	157-58	62	47.46 (47.53)	3.32 (3.37)	10.47 (10.42)
6'm	Hg	Br	4-OCH ₃	163-64	58	42.01 (42.04)	2.93 (2.98)	20.72 (20.76)
6'n	Od	Cl	4-OCH ₃	217-18	60	54.49 (54.60)	3.84 (3.87)	11.83 (11.96)
6'o	Od	I	4-OCH ₃	138-39	55	41.70 (41.73)	2.92 (2.96)	32.67 (32.71)
6'p	Hg	Cl	4 Cl	132-33	50	45.41 (45.47)	2.96 (2.91)	15.54 (15.52)
6'q	Hg	Br	4 Cl	118-19	45	40.23 (40.25)	2.51 (2.58)	20.66 (20.64)

TABLE V.6

STRUCTURE AND PHYSICAL PROPERTIES OF METAL-YLIDE COMPLEXES (6^a-q)

Product	M	X	R	m.p. °C	Yield %	Elemental analysis found (Calcd)%		
						C	H	X
1	2	3	4	5	6	7	8	9
6 ^a	Hg	Cl	H	194-95	53	25.81 (26.81)	2.18 (2.65)	15.99 (15.12)
6 ^b	Hg	Br	H	180-81	61	22.34 (22.19)	2.28 (2.21)	29.81 (29.59)
6 ^c	Cd	Cl	H	197-98	57	33.05 (33.02)	3.36 (3.30)	19.59 (19.53)
6 ^d	Ni	Cl	H	165(Dec)	57	38.78 (39.74)	3.39 (3.87)	22.98 (22.92)
6 ^e	Co	Cl	H	158-59	54	39.73 (39.31)	4.21 (3.87)	23.88 (23.43)
6 ^f	Hg	Cl	4-CH ₃	200(Dec)	64	28.34 (28.38)	3.11 (3.01)	15.82 (15.26)
6 ^g	Hg	Br	4-CH ₃	183-84	66	23.88 (23.82)	2.51 (2.52)	28.91 (28.88)
6 ^h	Cd	Cl	4-CH ₃	265(Dec)	58	34.90 (34.97)	3.80 (3.70)	18.99 (18.81)

1	2	3	4	5	6	7	8	9
6 [°] l	Cd	I	4-CH ₃	140-41	55	23.33 (23.55)	2.61 (2.49)	45.74 (45.32)
6 [°] j	Ni	Cl	4-CH ₃	160(Dec)	60	40.80 (40.77)	4.35 (4.32)	21.98 (21.93)
6 [°] k	Co	Cl	4-CH ₃	210-11	53	40.76 (40.74)	4.38 (4.32)	21.96 (21.91)
6 [°] l	Hg	Cl	4-OCH ₃	179-80	68	27.13 (27.44)	2.98 (2.91)	14.80 (14.76)
6 [°] m	Hg	Br	4-OCH ₃	180-81	66	23.67 (23.15)	2.45 (2.40)	28.87 (28.38)
6 [°] n	Cd	Cl	4-OCH ₃	260(Dec)	60	33.21 (33.55)	3.67 (3.54)	18.45 (18.05)
6 [°] o	Cd	I	4-OCH ₃	170-71	62	27.71 (27.70)	2.86 (2.93)	53.66 (53.31)
6 [°] p	Hg	Cl	4-Cl	171-72	58	26.67 (26.63)	2.41 (2.44)	15.81 (15.75)
6 [°] q	Hg	Br	4-Cl	151-52	55	22.44 (22.23)	2.08 (2.03)	29.67 (29.65)

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